UNIVERSITY OF TORONTO
MEDICAL JOURNAL

INFECTIOUS DISEASES

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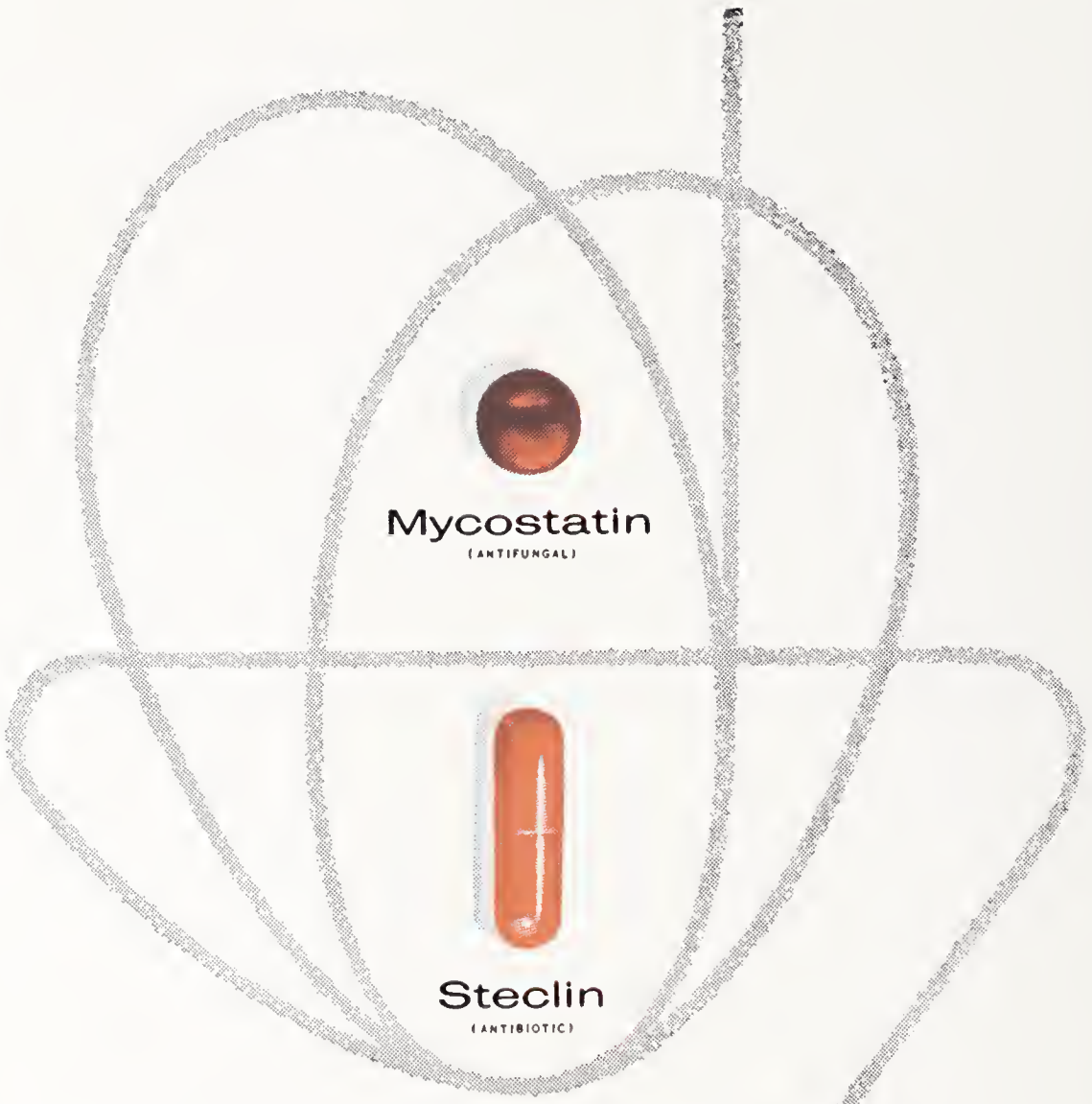

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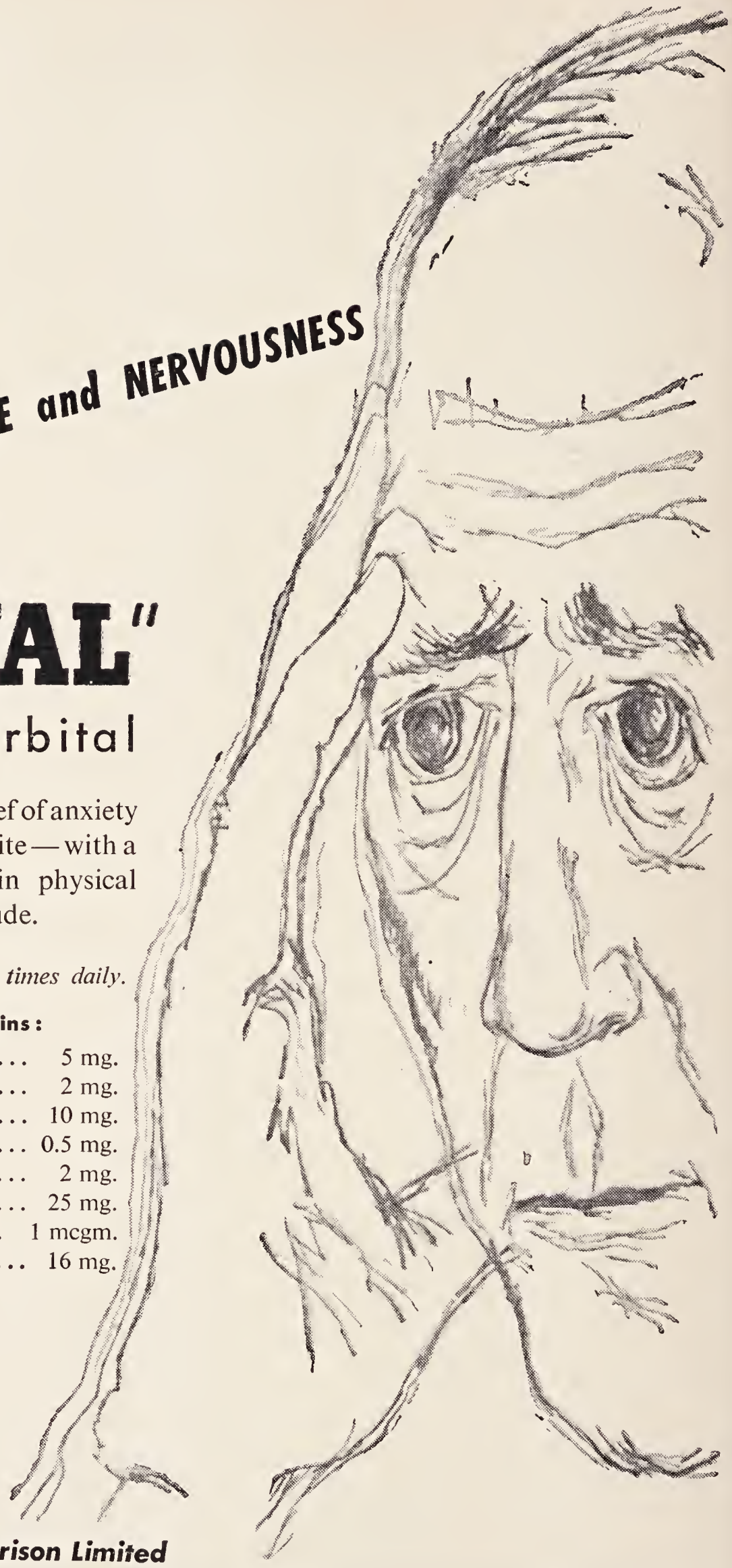

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Davis, C. H.: J.A.M.A. *157*:126 (Jan. 8) 1955.

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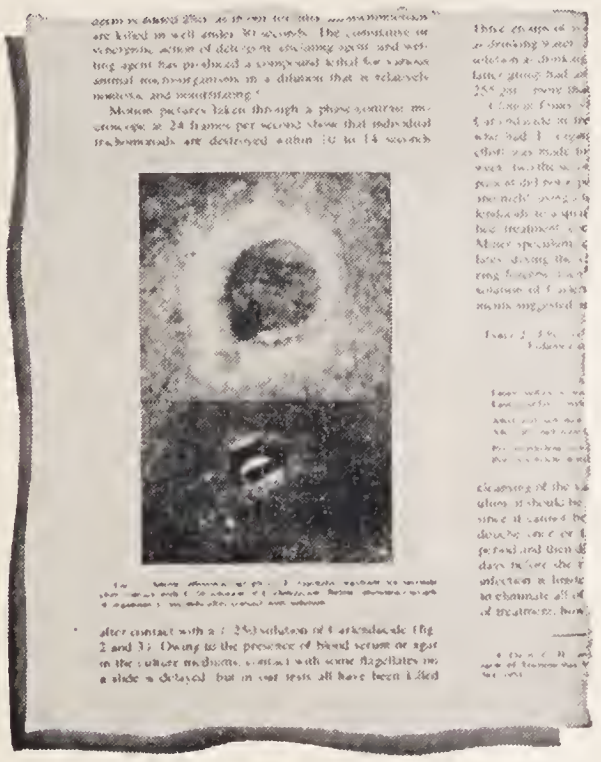

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Bibliography

1. Davis, C. H.: J.A.M.A. *157*:126 (Jan.8) 1955. 2. Davis, C. H.: Am. J. Obst. & Gynec. *68*:559 (Aug.) 1954. 3. Davis, C. H.: West. J. Surg. *63*:53 (Feb.) 1955. 4. Davis, C. H.: J.A.M.A. *92*:306 (Jan. 26) 1929.

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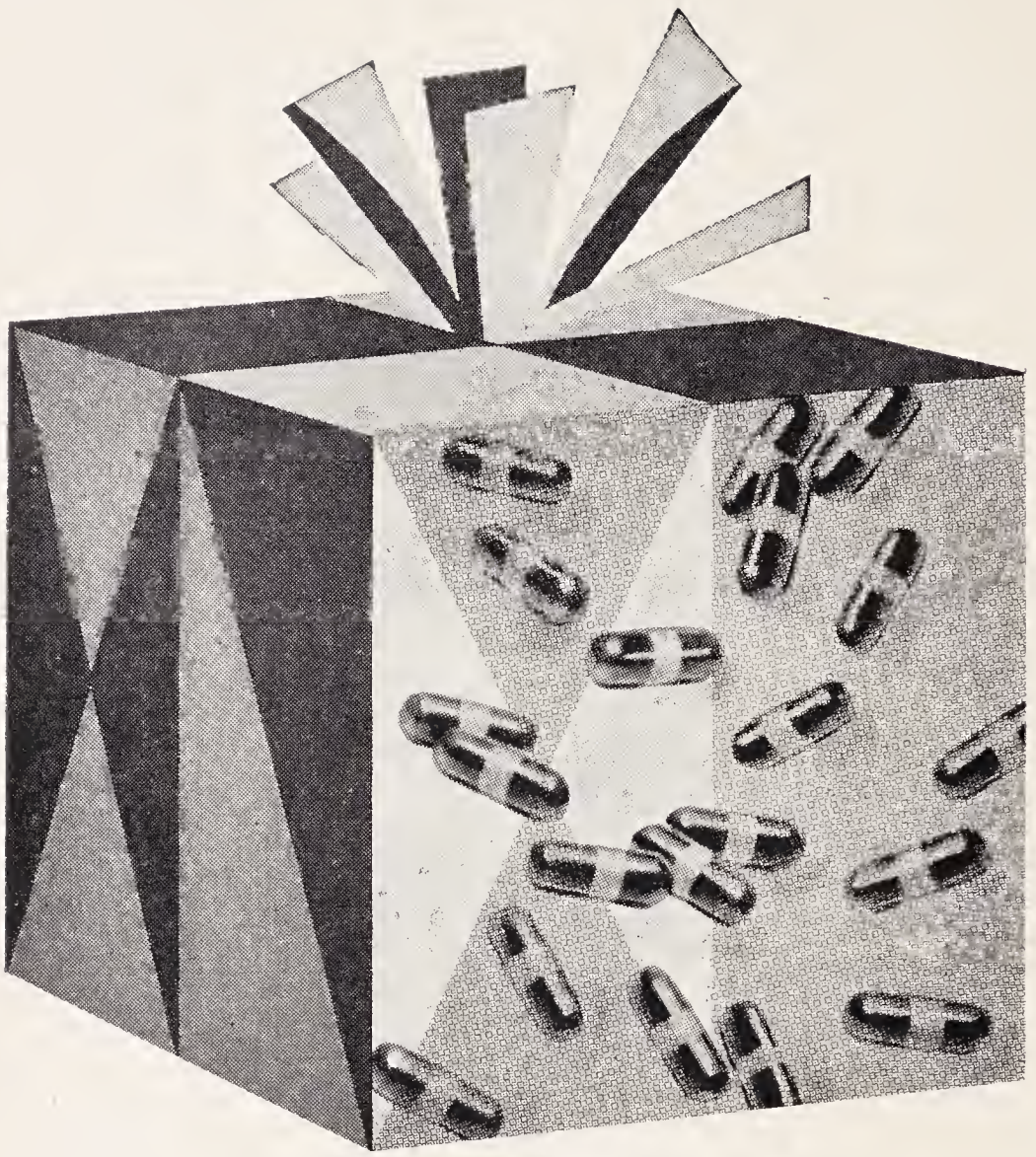

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EDITORIAL

Medicine and the Lay Press

In recent years, newspapers and magazines, to say nothing of radio and television, have taken an unaccountably intense interest in anything and everything related to medicine. Every daily paper has at least one medical columnist; every magazine or "digest" carries an inordinate amount of medical fact, lore, and fancy. Medical problems even appear in the comic strips. Indeed, it has become a class-room joke (not always bereft of either humour or wisdom) that if one is to keep apace of medical progress one must read any number of lay publications. It is not necessary to labour the point, because we are all familiar with it, but it might be worthwhile to consider some of the implications of this public obsession with medicine.

When a medical person considers the treatment of medicine in the lay press, his first expressions are usually vehement, and invariably critical. This is not without reason. The amount of medical misinformation propagated by the press is alone a justifiable ground for criticism. Further, the premature or injudicious release to the newspapers of progress in research, and the attendant misinterpretations, undoubtedly must raise false and even tragic hopes in some persons suffering from incurable disease. Finally, and perhaps most important in the overall picture, this undue concern with medicine may make hypochondriasis the commonest of all neuroses, if it has not done so already.

But we must not be too critical. The physician who in one breath decries all the copy in the public press dealing with medicine, in the next breath proclaims the urgent need for the public to be aware of the early symptoms of cancer. Obviously the public cannot be aware if it is not made aware, and the newspapers have long been recognized as one of the best media for informing. The family doctor cannot lecture each of his patients on all the early symptoms of cancer and other diseases: this teaching must be done through mass media.

When we re-examine the problem of the premature publication of progress in research, we again find two sides to the problem. Funds for medical research often depend upon the whims of public subscription, or at least upon the whims of public governments. And the public, reasonably enough, takes the attitude that if it is paying for research, it has a right to know how its money is being spent. The layman does not subscribe to research journals; he reads his daily paper. We are forced to admit, therefore, that if research is to survive it must be advertised at least to a degree in the lay press, regardless of what element of sensationalism may be attached to it.

We see, then, that current medical writing is doing the public both a service and a disservice. Can it be improved? Can the medical profession do anything to lessen the disservice while preserving the service? These questions are difficult to answer, but lately a new trend has appeared in the publicizing of medical

information which can do much to better the situation. This trend is toward more medical writing in the lay press which is authorized by official medieal bodies. For example, here in Toronto, the Ontario Medical Association has reeently sponsored forums on pertinent medieal problems which were broadcast and which subsequently were recorded in a loeal newspaper. These forums, free of sensationalism and misinformation, attracted enthusiastic public attention.

If this practice of authoritative sponsorship of public information is continued and expanded by the medical profession, then much of the abuse of medicine in the press can undoubtedly be eliminated. We must remember that perhaps no other profession has received so consistently so much criticism of its public relations. It is elearly time for the profession to take its public relations into its own hands.

J.Q.B.

THE PRESENT STATUS OF ANTIBACTERIAL THERAPY

K. J. R. WIGHTMAN, M.D., F.R.C.P.(C), F.A.C.P.*

MORTALITY and morbidity figures attest to the tremendous progress which has been made in the treatment of infections, although they also make it obvious that complete success has not yet been attained. The various chemotherapeutic and antibiotie agents which have made their appearance in the past two decades were discovered at a time when the medical world had just about decided that the approach which had proved so promising in the treatment of protozoal infections had nothing to offer in the fight against bacteria. It was natural then, that a great surge of optimism occured and high expectations of complete success were entertained. Not only have these hopes failed to be fulfilled, but new and unexpeeted problems have made their appearance. It has beeome perfectly elear that the strongest agents we have still depend for their success to a large degree upon the defense mechanisms of the patient, and will fail if these mechanisms are deficient. The remarkable freedom from toxic effects and side actions of many of these drugs has been offset by later manifestations of hypersensitivity producing severe and even fatal reactions. The relative specificity of their action and the exactness with which they must be used has imposed a burden of responsibility for accurate diagnosis and exact information on the members of the medical profession which they have been rather slow to recognize. For these reasons it would appear that an appraisal of the present status of this type of therapy should concern itself rather more with the difficulties and problems now facing us than with the success which has been attained and which is so obvious.

In the world to-day the aggregate cost of the antibiotics and chemotherapeutie agents produced per annum amounts to billions of dollars. It is therefore rather staggering to hear various authorities estimate that as much as 95 per eent of this total has been used in eircumstanees in which proof of its effectiveness ean-

*Associate Professor in Medicine and Therapeutics.

not be adduced. If this be true, it means that the profession is failing in its duty to keep down the cost of medical care, and also that patients are being exposed to risks which are not balanced by any tangible benefits.

Let us then examine the sources of this possible waste. I think it will become apparent that it results from a failure to apply certain principles which should govern this kind of therapy, and from a wide application of ideas which have not yet been established as being valid. One of the most contentious uses of these agents is in the field of prevention of infections. It is well known that very old and very young patients may succumb rapidly to infections, so that prevention is a justifiable aim. It is also evident that certain tissues of the body have a remarkably low resistance to infections and a very poor ability to overcome them, once established. Certain local or general factors can be identified in some patients which are known to increase the risks of infection to a marked degree. The fact that rheumatic fever and acute nephritis have become rather rare diseases is believed to be an indication of the effect of antibiotic therapy on streptococcal infections. Attempts at prophylaxis against a specific organism in either individuals or groups of people have seemed to be worth while when the risks were especially high. However, when we come to examine the results of widespread antibiotic therapy in the immediate postoperative period in patients who have had ordinary uncomplicated surgery and also in the treatment of patients with non-specific respiratory infections we find very little evidence that anything has been prevented. As a matter of fact not many proper studies of the problem have really been carried out. None the less, this type of treatment is very widely employed. Not only are these patients exposed to the risks of ordinary toxicity and sensitization, but also to certain other less obvious dangers which will be mentioned below.

In the treatment of established infections it seems quite probable that the dosage of antibotics used is often in excess of that required for the majority of cases. It is true that antibiotic therapy should be decisive and forceful in its early stages but once the patient has demonstrated a good response and once the possibility of various inimical factors has been ruled out, continuation with much smaller amounts would probably enable the patient to carry on with his convalescence without difficulty. The patient who has *not* responded in the first three days of treatment should be reinvestigated fully. Very frequently it turns out that he is not suffering from an infection at all, but rather from some other febrile illness such as Hodgkin's disease, carcinoma, pulmonary infarction, phlebitis, regional enteritis or a collagen disease, to name a few examples. Too often such a patient is left on antibiotic therapy when the investigation is inconclusive, sometimes for weeks. This too is wasteful and sometimes harmful. A trial of antibiotic therapy may be justified in any febrile illness, at least until a final diagnosis is established, but the end point of this trial should be defined in one's own mind as precisely as possible, and the antibiotic discontinued as soon as it is certain that no benefit has been produced.

The use of combined therapy with two or more agents has a place which is gradually becoming clearer. However, in many instances it merely represents a waste of one of the antibiotics used.

Finally, the use of troches and other local applications, usually without a

doctor's supervision, has also proved to be a wasteful and useless type of treatment.

It therefore appears that if this allegation of waste which has been levelled against us is to be countered or corrected we must undertake a more critical evaluation of our use of prophylactic therapy, especially in the postoperative period and in the treatment of non-specific respiratory infections. It is evident that we must make full use of whatever bacteriological facilities are available to us and to realize that in many instances the use of antibiotics without bacteriologic data is more or less comparable to taking out an appendix on the kitchen table. It may occasionally be necessary but it should be avoided whenever possible. In order to extract the maximum benefit it is obvious that we must work towards the most exact diagnosis possible, not only in clinical terms but also in such a manner as to allow us to visualize the pathological lesion present and all the factors which may influence our choice of antibiotic, the dosage needed, the duration of therapy, the possible need for combined therapy with two antibiotics or the likelihood that other types of treatment are also required. Thus we become aware of possible difficulties of diffusion of the antibiotic into the lesion, of difficulties in repairing the damage which is being done, of interference with phagocytosis and other local or general defense mechanisms, of disturbances of drainage, of the presence of necrotic tissue or thrombi in veins, and of the behaviour of the various tissues in response to infections.

Upon this background of facts about the patient we must superimpose what we know about the various antibiotics. As these agents multiply in number, so the difficulties of choosing among them become greater. Two attributes of any antibiotic which may become extremely important are its ability to diffuse into certain special tissues and the likelihood that it may exert a bacterioeidal rather than a bacteriostatic action against the organism concerned. Bacterioeidal antibiotics are preferable in any situation where the local tissue defenses are inherently poor, where they are poor because of pre-existing disease, where the infection is overwhelmingly severe, or where the general mechanisms of defense are impaired. The question of toxicity is a limiting factor in circumstances where extremely high blood levels are desired in order to permit diffusion of the antibiotic into an inaccessible area. In this case some method of parenteral administration for the antibiotic beeomes imperative, a difficulty which has been solved with respect to nearly all the important antibiotics of to-day. The effeet of the antibiotic on the normal bacterial flora of various parts of the body is important in reference to the phenomenon of superinfection—that is to say the establishment of a new infeetion due to an organism normally present in various areas of the body but usually restrained by competition with other organisms. If this balance becomes interfered with by the antibiotic given, a marked increase in prevalenee of the resistant species may occur, perhaps even with stimulation of its growth. It may then become a pathogen and introduce a most confusing element into the clinical picture. The superinfecting organism may also be an organism acquired from the environment—a resistant staphylococcus from the nasopharynx of one of the attendants of the patient in hospital, for example. This problem is one of increasing moment in our civilization to-day. It appears that superinfeetion is most likely to occur when treatment is prolonged and when an antibiotic or a

mixture of antibiotics is used which produces very marked effects on the flora of the bowel or respiratory tract, etc. The narrower the spectrum of the antibiotic and the more specific its action against the pathogen originally involved, the less likely is superinfection to occur. Its incidence is apparently greater in children and in persons who have some chronic lesion which lowers local resistance to infection in some area of the body, and thus allows the new pathogen an easy portal of entry. It is unfortunate that such superinfections may occur in patients whose original antibiotic therapy was not really well justified. They may prove fatal, unless their possibility is continually kept in mind and their diagnosis made by further bacteriologic investigation of the patient and treatment altered promptly.

The problem of resistant organisms already alluded to involves mainly such organisms as staphylococcus aureus, enterococcus, various of the coliform bacilli, as well as those organisms which have always been resistant to the agents we have yet developed, namely proteus, pseudomonas, pertussis, the yeasts and fungi, and the viruses. When resistance in the organism emerges during therapy it is still not quite clear whether it represents overgrowth of a strain which was originally present in small numbers or actually a mutation in the original strain. The fact that two antibiotics, streptomycin and erythromycin, seem to have an especially bad reputation in this regard appears to indicate that mutation may indeed play a part in some cases. The gradual emergence of resistant organisms in the population at large on the other hand is probably a matter of natural selection which again reflects the widespread use of antibiotics in the community. Certain antibiotics have been spared this fate, apparently because their use was not widespread. For example, chloramphenicol, whose unfortunate although occasional effects on marrow function led to a great reduction in its use for a time, appears to have been favoured as far as continued effectiveness against strains of staphylococci found in the general population and in hospitals is concerned. Be that as it may, it is certainly evident that our present fairly satisfactory state of control of infections has largely been the result of the succession of new antibiotics which have been developed as each one began to lose its power against the staphylococcus. Whether such a process can continue indefinitely remains to be seen. It does appear that if an antibiotic falls out of use for a time it once more becomes effective against the greater proportion of staphylococcal infections appearing in the populace.

Finally, we come to the problem of death due to antibiotic therapy. Preliminary animal experiments can indicate fairly clearly what direct toxic effects may occur when a new drug is developed, but fail to indicate what the risk of sensitization reactions may be in clinical use. In the case of penicillin there seemed to be almost no direct toxic effects. Then, as it was used in human beings it gradually became apparent that both local and general sensitivity reactions might develop, although these did not seem to be very severe. As more and more people became exposed to the drug and sensitized to it, the incidence of alarming and even fatal reactions began to rise. These took the shape of acute anaphylactic shock, exfoliative dermatitis which might persist for months and years, an illness like serum sickness which might also be extremely disabling for a long period, and finally, a progressive type of arteritis which appeared to be initiated by some reaction to penicillin but which persisted even after the drug had been removed,

and also eventually proved fatal. These serious reactions are now recurring with sufficient frequency to alarm both the profession and the public. The problem is how to detect patients who are likely to react in this way. In nearly all instances they have received penicillin before. No satisfactory method of skin testing has been devised so far, and the only course that one can follow is to avoid penicillin in patients who have had any sort of reaction to it before, however trivial, and to avoid giving it a second time to a person who has an allergic diathesis unless the indications are very strong. The use of antihistamine drugs or cortisone as a means of preventing the reactions has yet to be fully evaluated. In the long run it seems that two aspects of the problem await solution—first how to avoid sensitizing so many patients, and second how to detect this sensitization with certainty once it has occurred.

The gastrointestinal reactions to the broad spectrum antibioties also constitute a problem which has not yet been solved. In some cases, diarrhea etc. appear to be due to the direct irritating effect of the compound on the mucosa. In others a curious type of lesion is produced with shallow ulcers covered by a membrane. This can occur in the absence of antibiotics in seriously ill patients, especially in the postoperative period. However, its incidence appears to be increased by antibiotic therapy. The most serious bowel complication of broad spectrum antibiotic therapy is that caused by superinfection with resistant staphylococci. This can prove so rapidly fatal that its early recognition is imperative. The treatment consists in administration of a different antibiotic to which the organism is sensitive, along with fluid and electrolyte replacement. The diagnosis can often be made by examination of a stained smear of the feces.

The hematological effects of chloramphenicol, already alluded to, are probably also based on some hypersensitivity reaction to the drug, and may persist even when therapy is discontinued. Similar reactions to other antibioties have been reported but have received less publicity. The frequency of these disturbances is not great enough to prohibit the use of chloramphenicol in any condition where there is definite evidence that the patient's infection is serious enough to warrant antibiotic therapy and where it seems likely that the organism involved is sensitive.

In conclusion it can only be emphasized that the full fruits of these new discoveries can only be gathered if the scientific aspects of their use are thoroughly understood. We must also remember that we are not relieved of our "humanistic" obligations to our patients, even if the scientific part of their therapy is brilliantly conducted.

THE MANAGEMENT OF PULMONARY TUBERCULOSIS AT TORONTO HOSPITAL, WESTON

R. W. JACKSON, 5T6

AT the Toronto Hospital for Tuberculosis during the year 1954, 87% of the total admissions were suffering from some degree of pulmonary tuberculosis. Extra-pulmonary tuberculosis alone was present in 13%, and was found in association with 10% of the pulmonary cases. The procedures described, therefore, concern mainly the treatment of pulmonary tuberculosis. A brief outline of the ancillary services available at this hospital is included.

Specific Treatment

A. antimicrobial therapy

At the present time, Toronto Hospital, Weston, uses concurrently the three most potent drugs available in the fight against tuberculosis, although many other centres understandably use only two drugs at any one time and keep the third in reserve for use when deemed necessary. These three drugs, streptomycin, para-amino-salicylic acid (PAS), and isonicotinic acid hydrazide (INH) are used in the following dosages:

Streptomycin—1 gram intramuscularly twice a week

PAS—10 grams (14 grams of the sodium salt) orally daily (in 3 divided doses)

Isoniazid—300 mgms. orally daily (in 3 divided doses)

The duration of chemotherapy varies with the individual patient; but, as a general rule, a patient with minimal pulmonary tuberculosis receives 12 months of chemotherapy; moderately advanced pulmonary tuberculosis receives 12 to 15 months, and far advanced pulmonary tuberculosis receives 15 to 18 months as minimal periods. One long uninterrupted course of the 3 drugs tends to produce less resistance of the tubercle bacilli to the drugs than short interrupted courses. For this reason, the average stay in sanatorium for one course of treatment for those patients discharged in 1954 was approximately 16 months. Chemotherapy is commenced shortly after admission—as soon as sufficient specimens of sputum or fasting gastric contents have been obtained for routine examination.

The latest figures on the efficacy of the present 3 drug regimen shows a sputum conversion rate of 98% following 6 months of chemotherapy, as opposed to the previous 2 drug regimen conversion rate of 84%. There has also been a significant improvement in terms of cavity closure and radiological clearing. However, the long-term results of triple chemotherapy have yet to be assessed, as only three years have elapsed since this mode of treatment was started.

In an increasing number of cases during the last few months of therapy, drugs are being taken at home at the Government's expense. (Permission for this was granted by the Ontario Department of Health in May 1955.) This step may be considered following the completion of at least one year's treatment in sanatorium with consistently negative sputum for at least the latter six months. In most cases, the patient must bear the cost of the actual injection of the streptomycin himself.

A relatively small number of patients are unable to tolerate these drugs. If

*The writer was employed for three months during the recent summer vacation at Toronto Hospital, Weston.

toxie manifestations or sensitivity reactions oceur, the offending agent must be discontinued or serious complications may result. Drugs are withheld in less than 10 per cent of patients owing to hypersensitivity to PAS and in less than 1 per cent owing to hypersensitivity to streptomycin. Isoniazid is rarely an offender. An attempt is always made to desensitize the patient with gradually increasing dosage, and this method is usually successful. ACTH or cortisone may be tried to suppress the allergic reactions.

Several other drugs are useful in the treatment of selected cases of pulmonary tuberculosis. Among these are pyrazinamide and viomycin. Pyrazinamide is liable to damage the liver and frequent liver function tests are necessary. Viomycin is relatively weak in its action when used in a safe dose of 2 grams 2 or 3 times a week. A fairly recent development has been the use of cortisone or ACTH in combination with daily streptomycin, PAS and isoniazid. These are used only in selected cases which present in an acute, toxic condition with an exudative pneumonic type of disease. The clinical and radiological improvement in the few such cases so far has been striking, but it is still too early to draw definite conclusions.

B. SURGICAL TREATMENT

In spite of, or perhaps owing to the advent of modern chemotherapy, surgical treatment plays a major part in the management of approximately one-quarter of all patients with pulmonary tuberculosis. The two main aspects of surgical therapy are:

1. Collapse therapy
2. Resection therapy

Collapse Therapy

Underlying this method of treatment is the theory that the lung will heal better if put at rest. This is especially true in cases where cavities are present. Accordingly, both reversible and irreversible procedures are used for collapse, concurrently with, and as an aid to chemotherapy. Reversible procedures include:

1. Phrenic crush
2. Artificial pneumoperitoneum
3. Artificial pneumothorax

The use of these methods of collapse has declined greatly since the onset of chemotherapy, as it became plain that the benefits obtained by these methods were not worth the risks involved—particularly the functional impairment of the lung which may accompany prolonged artificial pneumothorax. The same benefits may be obtained by bed rest and chemotherapy, the ultimate goal in many cases being extirpation of the diseased areas. Phrenic crush is used now mainly at time of operation following pneumonectomy or lobectomy, in an attempt to reduce the residual space in the hemithorax. Pneumoperitoneum (with chemotherapy) may be established in ideal cases as a definitive treatment or to assist in obliterating residual pneumothorax. In 1954, only 7 pneumoperitoneums were established as compared with 25 in 1953. There have been no pneumothoraces established in the past 2½ years.

Irreversible collapse therapy is attained by the use of thoracoplasty. This involves the sub-periosteal removal of from 3 to 7 ribs, thus allowing the chest wall to collapse permanently. Thoracoplasty has also fallen out of use in recent years (4 standard thoracoplasties were performed in 1954 as opposed to 27 in 1953 and 95 in 1949) in favour of the less deforming operations of reseetion. Thoracoplasty is, however, still used as an adjunct to certain excisional operations, but solely for the purpose of reducing residual space and preventing over-expansion of remaining lung tissue.

Resection Therapy

The theory underlying resection therapy is that the patient has a better chance of complete recovery if the residual fibrocaseous diseased areas are removed, as many of these areas still contain live tubercle bacilli. With the use of modern chemotherapy, many patients who previously would have been unsuitable candidates for major thoracic surgery owing to the extent of their disease and to the possibility of spread can now be prepared by 6 to 9 months of drug therapy and then have the residual disease resected. The operations performed are pneumonectomies, lobectomies (multiple or single), segmental resections, wedge resections, and combinations of the latter three. The most common indications for resection are:

1. apical tuberculosis which was formerly treated by thoracoplasty
2. active lesions after failure of collapse therapy
3. bronchial stenosis with atelectasis and caseation distal to it
4. tuberculous bronchiectasis with positive sputum
5. a tuberculoma of doubtful stability or larger than 2 cm. in diameter
6. destroyed lung

It appears at the present that the optimum time for surgery is after 6 to 9 months of chemotherapy, and the 3 drugs are continued for six months after the operation. If bacterial resistance has developed, pyrazinamide with isoniazid may be used during the operative period and subsequently for 2 to 3 months.

Another surgical procedure that has produced excellent results is that of pleural decortication. It is used to free lungs that are trapped and unable to expand owing to a layer of fibrinous exudate which may have been laid down during artificial pneumothorax or as a result of tuberculous pleuritis. The operation is worthwhile in that it regains the function of otherwise healthy lungs, and prevents scoliosis. Decortication is also sometimes used in combination with resection.

C. BED REST

In recent years, there has been an increasing trend toward the allowance of more activity in the treatment of pulmonary tuberculosis. Part of this is due to improved methods of diagnosis and mass surveys whereby a larger proportion of patients who are clinically well are admitted with minimal disease. Those that are ill on admission improve so rapidly on chemotherapy that the majority of patients feel well throughout their stay in sanatorium. Consequently the number of patients on "total bed" is small, and the majority of patients are rapidly advanced through increasing exercise categories from "to bathroom once daily" to "full bathroom privileges" and later on to "dining-room privileges" once, twice or three times daily as their condition improves. The "average" case of pulmonary tuberculosis is allowed to attend one meal in the dining-room daily after about nine months of treatment. However, even for patients on full exercise, a minimum amount of rest with head on pillow is necessary, i.e. 1½ hours in the morning and 2 hours in the afternoon, with lights out at 9:30 p.m. Permission to leave the sanatorium for specified short periods of time is allowed at the doctor's discretion if there is no danger to the patient or to those with whom he comes in contact. Those patients with dining-room privileges are allowed one 12-hour pass or two 6-hour passes per month. Despite this trend toward increased activity, the basic theme in treatment is still rest.

Investigations

A. routine

Routine investigations performed on admission include a large 14″ x 17″ PA film of the chest and collection of sputum for examination on smear and culture for tubercle bacilli. If the patient has no sputum, fasting gastric contents are obtained for culture. These cultures are read at weekly intervals and considered negative if no growth appears in eight weeks. Routine urinalysis is also performed and the urine coneentrate is examined for and cultured for tubercle bacilli. Erythrocyte sedimentation rate, routine blood work and a blood Wasserman are done. If not previously done before admission, the Mantoux test using 1/20 mgm. Old Tuberculin is performed, and if negative, is repeated using 1 mgm. History and physical examination are done by the physician to whom the patient is assigned.

B. special

Following examination of the routine PA chest film, planograms may be taken of specified areas of the chest. Planography consists of a series of roentgenologic exposures taken at suceessively deeper levels of penetration through the chest. In these films, cavities arc sharply outlined, their location in the lung determined, and minimal lesions that were previously hidden by bony parts become clearly evident. Pulmonary function tests including bronchospirometry may be done as required. Bronchograms and bronchoseopy may be necessary for diagnostic purposes, and bronehoscopy is done routinely preoperatively. Sensitivity of the patient's tubercle baeilli to streptomycin, PAS and isoniazid are determined whenever a positive culture is obtained. These sensitivity reports are of importanee where chemotherapy seems to have little effect and a ehange may be indicated. Pathological examination is performed on biopsy specimens and specimens removed at operation.

Conferences

Regular daily conferences are held at the Toronto Hospital, Weston, which the entire medical staff attend. Eaeh of the staff physicians presents cases for discussion of further treatment, of the need for surgery, and of interesting or unusual developments. In this way, treatment is standardized and several opinions are obtained on each case. Similarly, before a patient can be discharged, his case must be presented at conference and his discharge approved by the majority of the staff. Every new admission is also reviewed at conference when the history, examination, x-rays and special investigations are completed. Here the proposed method of treatment is outlined, and some indication of the length of stay in sanatorium is given. Here also, the official diagnosis is made for the records.

One day a week is devoted to a clinico-pathological conference at which microscopic sections and gross specimens removed at operation or neeropsy are demonstrated and correlated with the clinical picture.

Ward Physician

The duties of the ward physicians are many, as each one is responsible for approximately 90 patients. Each patient is seen weekly, and the seriously ill are visited daily. Routinely, every patient is reviewed 7 weeks after admission and at 3-month intervals subsequently. These routine examinations include chest x-ray, sputum examination, physical examination, sedimentation rate and any other tests that may be indicated.

When these results are obtained, the patient is informed of his progress in a private interview and shown his x-rays. If there is some indication, these re-examinations are done at more frequent intervals.

A certain amount of the ward physician's work involves answering letters, preparing progress notes, completing forms and attending to other routine matters. He is responsible for the maintenance of discipline on his wards, and is often called upon to give personal advice to his patients. He is also obliged to send regular reports to the family physicians of patients under his care, and prepare discharge summaries at the time of discharge or death.

Associated Services

Available to all patients admitted to the sanatorium are a routine dental examination and a routine gynecological examination (for women over 30). The services of an optometrist are also available for those who request it. Consultants in internal medicine, thoracic and orthopedic surgery, genito-urinary surgery, gynecology and psychiatry are also available. These consultants hold regular clinics (psychiatry excepted) to which difficult or interesting problems may be brought by the medical staff.

Recreational and Vocational Facilities

Many facilities are available for recreation. Movies are shown regularly in the Assembly Hall and on the wards. Television sets are scattered throughout the hospital. Stage shows are presented by the patients themselves, and a well-stocked mobile library is available to all. The hospital also has its own radio station which is operated entirely by the patients and is received at each bedside through ear-phones. During the hours of activity, the station broadcasts a variety of musical shows, quiz programs, medical information about tuberculosis, hospital news, and so on. Also, the patients and staff jointly publish a popular monthly magazine which contains hospital news and information. Most of these activities are governed by the Patients' Council which has elected representatives from each ward.

For the individual, there are many restful diversions to help spend the long hours. Occupational therapy offers leather and copper work, painting, and handicrafts of all types. The hospital school is capable of teaching at the bedside any grades from one to 13, and even technical and commercial courses within reason are available.

The rehabilitation of the patient is assisted by a special committee which interviews the patient during his stay, and reviews his case in a special conference at time of discharge. The case is then referred to the Rehabilitation Officer of the Department of Health in Ontario, and further courses may be arranged.

Summary

An attempt has been made to acquaint the reader with some of the modern procedures and methods used in the treatment of pulmonary tuberculosis at the Toronto Hospital for Tuberculosis, Weston, Ontario. In addition to the medical, surgical, and nursing care provided. much attention is paid to the rehabilitation of the patients, as well as to their recreational and social needs. At Weston, the duration of treatment has changed very slightly since the use of chemotherapy. It is hoped that the regimen of long-term triple chemotherapy, combined with the judicious use of surgical treatment, will markedly reduce the relapse rate.

Acknowledgments

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INFECTIOUS HEPATITIS: DIETARY ASPECTS

P. D. HOPKINS 5T6

INFECTIOUS hepatitis is an acute disease of viral origin which usually occurs sporadically, but may appear as an epidemic in the Services or where masses of people are brought together. Homologous serum jaundice is a parallel disease whose signs, symptoms, and laboratory data are the same.

Prior to the advent of liver biopsy techniques the pathological lesion was thought to be, as Virchow originally described, an ascending catarrhal inflammation of the biliary ducts. We now know that the essential lesion is composed of diffuse swollen and degenerated hepatic parenchymal cells, with or without portal and periportal damage. The extent of liver cell involvement is mirrored by the clinical picture, which ranges from a mild anicteric disease which runs a benign course, to the very uncommon, severe acute fulminating case with rapidly deepening jaundice, drowsiness, coma and death.

Differentiation of acute infectious hepatitis (I.H.) from homologous serum jaundice (S.H.) can be made only after isolation of the virus from stool, and measurement of the incubation period, which in I.H. is 18–30 days, and in S.H. is 60–120 days. History of previous transfusion may give the clue. Diagnosis of viral hepatitis should not be difficult if proper attention is paid to the history, which gives a picture of anorexia (in 82% of 200 cases reported by Havens in the Middle East, 1942–44, and in 95% of 454 cases in Korea and Japan reported by Chalmers *et al.*, 1951–52). General malaise, fever, chills, nausea, vomiting and upper abdominal pain are often prominent. Dark urine, with or without pale stools is often the first symptom complained of, but may frequently be absent.

Physical examination may or may not add helpful information. Icterus is common but not infrequently it may be confined only to the sclerae, and that may be detected with difficulty if minimal, or not at all under artificial light. It must be remembered that the prodromal or pre-icteric phase of infectious hepatitis varies widely, and laboratory investigations undertaken at this time may be normal.

Liver tenderness with or without enlargement is a valuable sign in diagnosis. Splenomegaly, lymphadenopathy and spider telangiectasia are inconstant findings.

THERAPY

In 1918 Osler suggested, "simple diet and restricted fats; a dose of calomel and subsequent salines may be added to keep open the bowels. Irrigation of the colon with cold water is supposed to excite peristalsis of the gall bladder and ducts and aid in the expulsion of mucus." Now, as in 1918, there is still no specific therapy for infectious hepatitis, but with our present knowledge of the essential pathology and more accurate means of diagnosis, we are able to shorten the duration of illness and reduce complications. In the years before 1940, this condition was treated most casually. During the Second World War, however, a great deal of information was gathered on military personnel who contracted I.H. and S.H. in Europe, the Mediterranean and Near East, by U.S., British and Canadian medical officers.

Controversy over prolonged bed rest versus early ambulation, optimal diets and the proportion and quality of fat and protein, high versus low calorie diets, and forced versus ad lib diets, has clouded the literature for years.

Bed rest at one time was prolonged until liver function tests and clinical signs returned to normal. More recently, with more investigation and experience, such conservatism has given way to shorter periods of enforced bed rest. The question of diet, particularly with regard to efficacy of contents, quantity and specific supplements, has been speculated about and argued over for 15 years. The effects of fat, protein and caloric values on the duration of illness have been debated in numerous studies.

Leone, after conducting controlled studies on prison inmate volunteers previously inoculated with virus of serum hepatitis, concluded that:

1. The average duration of illness of patients on "ad lib." (i.e. prison fare) diets was significantly shorter than that of patients on the high protein (200 Gm.) high carbohydrate (680 Gm.) and low fat (25 Gm.) regimen.
2. The occurrence of complications was more frequent among patients with the high protein and carbohydrate, low fat diets.

Darmady was unable to demonstrate the effectiveness of high protein dietary therapy.

Hoagland, in a series too small for statistical validity, concentrated on the problem of low fat versus relatively high fat diets, with high protein and carbohydrate. He concluded that 150 Gm. of butterfat per day (milk, cream and butter) in conjunction with proteins and carbohydrates:

1. Aided patients to take in more calories with less carbohydrate bulk than did the low fat diet;
2. Caused an immediate weight gain as compared to low fat diet.
3. Caused an earlier return of bromsulphalein tests to normal.
4. Created a more palatable diet with less secondary anorexia.

Hoagland also pointed out that in experimental animals with choline deficiency, milk fat products with carbon chains of less than 12 produced less hepatic fatty infiltration than fats whose carbon chains ranged from 14–18. We know now that the pathological lesion in the livers of patients suffering from infectious hepatitis is not one of fatty infiltration. However, in the rare cases which may go on to chronic hepatitis with ultimate cirrhosis, such a factor as "good" dietary fat may be worth keeping in mind.

The views presented by the three preceding authors were typical of the state of affairs until Chalmers, in a carefully designed and well-controlled study of 460 army patients at the "Hepatitis

Centre" Kyoto, Japan, published significant results in July, 1955.

The difficulties that all investigations have encountered are:

1. Criteria for admission to investigation.
2. Great variability in disease, with manifestations in clinical signs and laboratory data, and concomitant difficulty in measuring treatment effect.
3. Adequate follow-up examinations.

CHALMERS' FIRST STUDY: RELATIVE EFFECTS OF DIET AND TEST ON DURATION OF ILLNESS

Selection of Patients:

1. Male members of U.S. Armed forces.
2. Required to have clinical jaundice or persistent darkening of the urine with probable diagnosis of I.H. by Study Medical Officers.
3. Pre-admission duration of symptoms of less than 22 days.
4. No evidence of various disease states.
5. No previous plasma or blood within 6 months.
6. No previous I.H. within one year.

Criteria for Measuring Treatment Effects:

The "duration of illness" was arbitrarily chosen to be the time from admission to the hospital to start of progressive ambulation for the strict bed rest group, and an equivalent period of time for the "ad lib" rest group (i.e. when one normal bromsulphalein test of 5% was obtained or two out of three semi-weekly serum bilirubin tests were 1.5 mg.% or less).

Effect of Randomization:

Thirty-four variables (under medical history, admission physical examination, admission liver function tests) were examined. The distributions of all the others, known and unknown, were left to chance by assigning patients to treatment wards using random numbers.

Two hundred and sixty patients underwent therapeutic tests of diet and rest. Half were on "ad lib." diet and half on forced diet; half were on "ad lib." rest and half were kept in bed. The influence of one factor on the other could then be measured.

1. *Forced High Protein Diet* (3,000 calories minimum with 150 Gm. of protein)

Fat and carbohydrates were allowed to seek their own level. The mean dietary composition of the patients' meals was: 4060 calories, of which 20% was protein, 35% carbohydrate and 45% fat.

Choline dihydrogen citrate 3.9 Gm. plus 6 multivitamin tablets daily were also given. Patients were forced to reach the established minimum (3,000 calories with 150 Gm. protein) regardless of anorexia. Those failing to do so were tube-fed. Six patients only were initially tube-fed, and it was thought that this procedure in the ward was an enhanced stimulus for the other anorectic patients.

2. *"Ad Lib." Diet*

Patients were served standard military hospital diet without attempt to maintain caloric level.

3. *"Ad Lib." Rest*

The level of patient activity was not controlled, and patients were allowed out of their beds as much as they desired, with one stipulation—that they rest in bed for an hour following meals.

4. *Strict Bed Rest*

Patients remained in bed except for a daily trip to the bathroom and a twice-weekly shower.

Summary of Results

1. Checks on the randomization method revealed that it was effective.
2. (a) Patients on "ad lib." rest had slightly shorter duration of illness.
   (b) Patients on forced high protein diet with supplement had a 22% reduction in duration of illness.
   (c) There was no interaction between diet and rest.
3. Asymptomatic bromsulphalein relapses occurred in 7% of patients with equal group incidence.
4. (a) A significantly more rapid fall of mean serum bilirubin in the forced diet group was noted.
   (b) There was a tendency for flocculation and turbidity tests to be more abnormal in the forced diet group at the end of the acute illness, but tests were the same in both groups at time of discharge.
5. Various treatments had no striking effects on patients' signs and symptoms.

CHALMERS' SECOND STUDY

Finding the significant reduction in the duration of illness from the forced diet, it was necessary to discover which of the three dietary factors—total calories, protein or choline vitamin supplement—was responsible. A second study was made.

Admission criteria were the same and 168 patients were admitted to treatment. All patients were allowed out of bed "ad lib" except for the one hour postprandial rest.

Make-up

High Caloric Diet (C)—4,000 calories.
Normal " " (c)—3,000 calories.
High Protein Diet (P)—19%
Normal " " (p)—11%

Half of the patients received 3.96 Gm. of choline dihydrogen citrate plus 6 multivitamin tablets (S) daily and the other half received placebo (s).

There were therefore eight treatment groups:
CPS, cPs, Cps, cpS
CPs, cPS, CpS, cps.

Summary of Results

1. Patients fed the high protein diet had a mean duration of illness 14% shorter than those fed the "normal" protein diet.
2. Patients fed the high calorie diet did not have a significantly shorter duration of illness than those fed the "normal" calorie diet.
3. Patients fed supplemental choline and vitamins did not have a significantly shorter duration of illness than patients receiving placebo.
4. No demonstrable interaction among the three dietary factors was found.
5. Asymptomatic bromsulphalein relapses occurred in 4% of patients without any significant distribution in the treatment groups.
6. Significantly more rapid falls in total and prompt indirect serum bilirubin levels in high protein groups were found in comparison to "normal" protein groups.

Follow Up Examination

Complete information was obtained on 176 of the original 460 patients. It was found that:

1. Patients on "ad lib" rest regimen had more individual abnormalities than those on strict bed rest. These abnormalities, however, had no clinical signicance.
2. No difference was found between patients of the 1st Study with forced high protein diet and those with "ad lib" diets.

3. Patients in the 2nd Study from the high protein, high calorie group showed more definite abnormalities than patients from the other groups. However, subsequent hospitalization of 11 "abnormals" showed all but one to be essentially normal.
4. Comparing 147 former patients with normal "controls" an increased frequency of liver pain, hepatomegaly, and spider telangiectases was found, but liver function tests were normal.

The recommendations, in part, which followed these findings were presented to the Surgeons General of the Armed Forees:

1. *Rest*

Patients may be allowed out of bed as soon as they feel well regardless of the degree of jaundice. An enforced rest of one hour after meals is desirable. Such "ad lib" activity shortens recuperation, which is lengthy after a prolonged stay in bed. Violent physical exertion should be avoided.

2. *Diet*

(a) 3,000 calories with 150 Gm. each of protein and fat. The fats should be from dairy products and eggs.
(b) If the patient is severely anorectic, frequent small feedings with addition of enriched milk shakes should be given.
(c) If hospitalization time is important (as in the Armed Services during an epidemic) forced tube feeding should be used on patients who do not reach the dietary minimum.
(d) Parenteral glucose must be instituted if patient is nauseated and vomiting.
(e) It is important to remember that in the severely ill patient, with impending hepatic coma, proteins must be kept at maintenance level only.

Summary

A review of the literature of the past ten years has been made, in an attempt to find valid statistical evidence for a specifically modified diet in the treatment of infectious hepatitis.

Acknowledgment

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INFECTIOUS MONONUCLEOSIS

D. E. F. GREENHOW, 5T6

INFECTIOUS mononucleosis is an acute, self-limiting, rarely fatal, generalized infectious disease, probably caused by a virus. It is characterized clinically by fever, lymphadenopathy, symptoms of an acute respiratory infection, other symptoms of an extremely diverse nature, and atypical lymphocytes in the circulating blood.

HISTORY

Infectious mononucleosis first appeared as a clinical entity about seventy years ago. Its history may be divided into four periods. From 1885 to 1920 the disease was described clinically as glandular fever. There are several reports of spontaneous cures of lymphatic leukemia during this era. These were discussed as perhaps being glandular fever. The period from 1920 to 1932 was marked by the delineation of the blood changes, and the first use of the name infectious mononucleosis. The third period began in 1932 with the fortuitous discovery by Paul and Bunnell of the heterophile antibody. It lasted until 1944, when autopsy reports began to appear in the literature. From 1944 until the present time extensive investigation has given us a greater understanding of the pathology of the disease.

INCIDENCE

Infectious mononucleosis almost always occurs in young adults and children. It is rarely seen after thirty-six years of age. Eighty per cent of cases occur between the ages of fifteen and thirty.[1] Infection in males predominates in a proportion of three to two. Perhaps this is because it is diagnosed more often in medical students and internes than in the general population. It has a world wide distribution, but until recently few cases had been reported in Negroes.

ETIOLOGY

A virus seems to be the most likely causative agent. L. monocytogenes hominis has been incriminated, but there is little proof of its guilt. The agent, whatever it is, has never been transmitted in the laboratory.

PATHOLOGY

Since recovery is almost universal in infectious mononucleosis autopsy reports are rare. Those which do exist indicate that it is a generalized disease with infiltration of almost every organ of the body.

Gross changes are confined almost entirely to enlargement of the lymphoid tissues, especially the spleen. Nasopharyngeal hyperplasia was constant in one series. Other gross changes reported are consistent hepatomegaly, infrequent icterus, and occasional rash.

There is infiltration of all tissues except the bone marrow by normal and abnormal lymphocytes. This infiltration is characteristically in a perivascular arrangement, similar to that in known virus disease. The spleen also shows more primitive cells—lymphoblasts and stem cells. The liver and spleen are enlarged solely because of infiltration by these cells. Jaundice, when seen, is due to extensive focal hepatitis. In some reported cases, reticuloendothelial hyperplasia was so marked that the disease resembled a lymphoma. Myocardial infiltration explains the electrocardiographic changes seen occasionally. Meningoencephalitis from infiltration of lymphocytes has been seen.

SIGNS AND SYMPTOMS

Signs and symptoms are extremely variable in both nature and severity. Some patients may be entirely asymptomatic, while others may be extremely ill. However, the following characteristics are fairly constant:

1. Most patients have fever, enlarged and slightly tender lymph nodes, and some symptoms of an acute respiratory infection.
2. The disease is confined as a rule to children, adolescents, and young adults.
3. It has a long morbidity.

In the prodomal stage, usually of three to six days duration, the symptoms are vague and non-specific, with insidious onset. Malaise, headaches, mild aches and pains, fever, chilly sensations (but rarely true rigors), sore throat, and other manifestations of an upper respiratory infection are characteristic. The temperature curve is irregular, but rises late each afternoon. In this stage the disease is often diagnosed conveniently as "flu."

In the mid-stage, the clinical picture becomes more characteristic, but the manifestations are still very diverse. Cervical lymphadenopathy is practically universal, and there is often generalized lymphadenopathy as well. The nodes are slightly tender, varying in diameter from 0.5 to 2 cm. They are non-adherent, firm, and never suppurate unless secondarily infected. Sore throat is very common, and characteristically the patient complains of a gritty, lumpy feeling. The pharynx, soft palate, uvula, and pillars are brilliant red in colour, and the soft palate and uvula have a translucent edema. However, the nasopharyngeal symptoms may vary from mild rhinitis or pharyngitis to follicular or membranous tonsillitis, or Vincent's angina if the throat is secondarily infected. Splenomegaly occurs in 50 per cent of cases. Usually the enlargement is slight, but occasionally is great.

Headache occurs in three-quarters of all cases. It may be so severe as to be the presenting symptom. One-quarter of all cases have stiff neck, and some may even have a positive Kernig sign. There may be serious neurological manifestations, but these have a uniformly good prognosis.

In about 20% of one series a finely macular cutaneous rash was seen, involving first the trunk, then the face. There was no pruritus. The rash appeared anytime from the third to the twentieth day, and lasted three to seven days, without desquamation.

Persistent abdominal pain was present in 16 to 18 per cent of cases, and nausea and vomiting in 12 per cent. Appendectomy has been performed. The cause of abdominal pain may be the swelling of spleen or mesenteric lymph nodes. Possibly some cases of mesenteric lymphadenitis are part of the syndrome of infectious mononucleosis.

Jaundice occurs in 10 per cent of cases and as a rule is mild. It is due to extensive focal hepatitis, or in very rare cases, to hemolytic anemia. Three clinical types of infectious mononucleosis with jaundice are described:[2]

1. Jaundice occurring first, then glandular enlargement.
2. Jaundice with glandular enlargement.
3. Jaundice with or without fever.

Although icterus is not universally seen, abnormal liver tests are found in 90 per cent of cases.

It has been reported[3] that 2½ per cent of cases show pulmonary lesions similar to those of virus pneumonia.

The convalescent stage customarily lasts from two to three weeks, but may be much prolonged. During this time the only symptom is easy fatigability.

Sometimes the clinical picture of in-

fectious mononucleosis is classified under headings which emphasize the system particularly involved: glandular form, anginose type, or febrile type. However, this differentiation is an artificial one, for there are all variations of symptoms, with much overlapping among the three types.

BLOOD CHANGES

The most striking change in the blood picture is the appearance of abnormal cells which comprise at least 50 per cent of the total white blood cells in all cases, and between 60 to 90 per cent in three-quarters of all cases. Downey, in an early paper,[4] described three types of these cells and his description is still applicable today:

1. Cells characterized by heavy staining, irregular or bean-shaped nuclei without nucleoli, and dark blue foamy cytoplasm.
2. Cells characterized by relatively large amounts of light blue cytoplasm and a normal appearing eccentric nucleus.
3. Cells characterized by their resemblance to malignant or leukemic cells. These occur much less often.

The striking feature of the smear is the unending variation in the appearance of the abnormal lymphocytes. No two look alike. They can vary from normal appearing mature lymphocytes to huge bizzare cells. This is very different from acute leukemia or chronic lymphatic leukemia where there is a dreadful monotony in the appearance of the cells.

Often there is a leukopenia in the first week which may be as low as 1500 to 2500. In one-third of cases the white cell count does not go above 10,000 at any time, although the usual count is between 10,000 and 20,000.

The abnormal cells usually disappear in a few weeks, but not rarely last for three to six months. One case was reported with characteristic cells persisting for ten years.

The platelets and red blood cells are practically always normal in appearance and number.

In spite of the generalized infiltration, the bone marrow is not involved, although it appears to have slight myeloid hyperplasia and is generally immature.

Sheep cell agglutinins are found in high titre in 60 per cent of cases. Many normal people have these agglutinins in a dilution of 1:16, and many patients with viral hepatitis have them to a high titre. In the second and third weeks, the titre rises to 1:256 and may be as high as 1:2000. It should not be considered as a diagnostic aid unless it is positive to a dilution of 1:64. These agglutinins may appear several days prior to the blood cell changes, or may not appear until quite late in the course of the disease. The reaction becomes negative within three months as a rule.

False positive tests for syphilis occur in about 18–20 per cent of patients with infectious mononucleosis.

DIFFERENTIAL DIAGNOSIS

The only safe course from a diagnostic viewpoint is to consider infectious mononucleosis in the differential diagnosis of every febrile condition of obscure nature in young people. It can be confused with Hodgkin's disease, acute lymphatic leukemia, acute lymphocytosis, acute tonsillitis, Vincent's angina, secondary syphilis, agranulocytosis, acute infectious hepatitis, encephalitis, meningitits, poliomyelitis, the Guillain-Barré syndrome, and conditions with skin manifestations such as German measles and scarlet fever. Practically every viral disease has been known to have atypical lymphocytes similar to those of infectious mononucleosis, but rarely in as great a concentration. If they are present diagnosis can be very difficult.

The following rules should be kept in mind in differential diagnosis:

1. Incorrect diagnosis may be avoided by a sufficient period of observation.
2. The condition is limited to children and young adults.
3. The characteristic signs of infectious mononucleosis may be delayed for the first week, but eventually at least two and usually three will appear.

Perhaps some may think that a diagnosis is merely of academic interest in difficult cases since infectious mononucleosis is such a benign disease. However, it is of great importance from a prognostic viewpoint for two reasons. First, the patient must be warned that he will possibly feel ill for several weeks. Second, it must be differentiated from acute leukemia or chronic lymphatic leukemia with their hopeless prognosis. If upon history, physical examination, and examination of the smear differentiation from leukemia is still not possible, bone marrow aspiration should be performed. This will almost invariaby give a diagnosis if the disease is leukemia.

PROGNOSIS

The average case runs its acute course in ten days to two weeks, but often may be greatly protracted. Following this there is a period of convalescence lasting from two to three weeks. Deaths have been reported in infectious mononucleosis, but when the great incidence of the disease is considered it may be seen that it is rarely severe, and only in exceedingly rare instances does it prove fatal. While rupture of the spleen is often mentioned as a cause of death, only thirteen cases with this complication had been reported by 1948, and the mortality rate in these was about 50 per cent.

In some cases where recovery seems complete, relapse occurs several weeks or months later. Relapse is more likely to occur if the patient has been asymptomatic but still has an elevated leukocyte count and lowered polymorphonuclear count when permitted to return to normal activities. This could hardly be called a relapse, but rather an extension of the disease. If a patient waits until the blood picture is normal before resuming normal activities relapses never occur.

THERAPY

There is no known specific therapy. When the tetracycline group of antibiotics first appeared, some investigators reported success in the treatment of infectious mononucleosis, but repeated studies have failed to show any beneficial results with any antibiotic. Serious manifestations can be prevented by complete rest early in the disease. Symptomatic therapy with salycilates or codeine may be used. The possibility of secondary invaders should be remembered.

SUMMARY

Infectious mononucleosis has been considered under the headings of history, incidence, etiology, pathology, symptomatology, diagnosis, prognosis, and therapy. Its manifestations are protean. The causative agent is unknown. There is no specific therapy. Much more investigation is required before specific conclusions can be drawn regarding the many problems involved in this disease. Perhaps we shall find eventually that infectious mononucleosis is not one disease, but a spectrum of diseases.

ACKNOWLEDGMENT

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THE COMMON COLD

F. B. ROBERTS, 5T6

INDUSTRIAL workers lose on the average two days per year from colds, millions of dollars annually are spent needlessly on antibiotics, and yet for the laiety and the profession the common cold has remained an enigma. Knowledge about this ubiquitous disease is, however, advancing and the medical practitioner should be aware of the facts that laboratory investigation has revealed.

ETIOLOGY OF THE COMMON COLD

Since 1917 repeated efforts have been made to isolate the causal agent of the common cold and, more recently, the introduction of tissue cultivation techniques in virology have given fresh impetus to the search. A review of various studies which are recorded below illustrates three features:

1. The virus is elusive and difficult to cultivate or isolate.
2. The lack of susceptible laboratory animals has proved a serious obstacle to experimental study.
3. The necessity of using human volunteers has greatly limited experimental procedures, and the inability to determine, previous to inoculation, whether or not a volunteer is susceptible to infection has produced erratic and poorly reproducible experimental data.

In the history of the investigation of the common cold studies undertaken by G. B. Forster in 1917 at the Harvard Medical School Laboratory in Arizona are outstanding. Dr. Forster observed that, despite the supposed bacterial etiology of the common cold, nasal secretions in early cases were almost sterile. Three years previously a German, Kruse, had transmitted colds to 19 of 48 volunteers by the intranasal instillation of bacteria-free Berkefeld filtrates of nasal secretions. Aware of Kruse's work, Forster transmitted colds in a similar manner to 7 of 10 subjects. The next step was cultivation of this filter-passing agent.

Only after developing a fastidious technique did Forster succeed in preparing a sterile, anaerobic, rabbit kidney-ascitic fluid culture medium. This he inoculated with Berkefeld filtrates of nasal secretions from a patient with a cold. On incubation he observed with a hand lens a growth of minute particles in the fluid above the kidney tissue. When smeared and stained these particles appeared to be aggregates of smaller "coccoid bodies" about one-fifth of a micron in size; he included in his report a photomicrograph of these coccoid bodies. He refiltered the growth from the first generation, reinoculated a second series of culture tubes and grew a heavier second generation crop. The second crop he filtered and inoculated into 11 subjects, 10 of whom developed full-blown colds. Since the original constituents had been diluted over 90,000 times before inoculation of the volunteers, and the second generation growth was more abundant, Forster concluded that the agent responsible for the common cold must have grown in the culture medium. He felt, however, that the coccoid bodies, which appeared in each subculture but not in his controls, were produced by an ultramicroscopic agent (Noguchi and Flexner working at this time had isolated similar "globoid bodies" from cases of poliomyelitis). Forster's work almost forty years ago has been until the present day a model for subsequent investigators.

The scene then shifted to Columbia

University where in 1931 Doehez and eollaborators reported the sueeessful eultivation of a eomon eold virus in anaerobic tissue eulture of mineed chiek embryo. Five years later they subeultured a virus through fifty generations over a period of 159 days, the last generation being still infeetive.

Meanwhile Powell and Clowes (1931) eonfirmed Forster's work and later there were many reports of the sueeessful eulture of eommon eold viruses in egg embryo allantoie fluid (Topping and Atlas 1947; Pollard and Caplovitz 1947; Ward and Proctor 1950; Reagen 1954). It now seemed well established that the eommon eold virus, or viruses, could be readily grown both in tissue eulture and on the ehiek embryo allantoie membrane. The stage was set for rapid advances.

In 1946 the Medieal Researeh Counеil of England and the Ministry of Health established the Harvard Hospital Common Cold Researeh Unit ninety miles from London. The hospital had twelve isolated units, eaeh aeeommodating two subjeets; during the first four years fifteen hundred people were inoculated. The subjeets were isolated in pairs, seen only by a matron and doetor, both of whom were eapped, masked and gowned. The volunteers were kept isolated for a preliminary three days to exelude an ineubating eold before they were inoeulated (by intranasal instillation) with the material being tested. The elinieal investigators did not know the nature of the test material or the identity of controls before thev decided whether a eold had developed.

Then began the simple task of cultivating a eommon eold virus. Dr. Andrewes, the direetor, made repeated attempts to grow a virus in tissue eulture, as Doehez had, and to grow it in egg allantoie fluid, as Topping and Atlas had; but eaeh attempt was unsueeessful. Dr. Andrewes feels that he will, in time, stumble on a strain of eommon eold virus whieh will grow on egg embryo media for there have been many reports of sueeessful eultivations by reliable observers on this eontinent. This is eertainly a puzzling and unexpeeted problem. However, two years ago Andrewes did sueceed in subculturing through ten generations a common eold virus on a tissue eulture of human embryonic lung.

As yet no eommon labratory animal has been found to be suseeptible to a eommon eold virus; only man and the ehimpanzee ean be infected. Reeently interest has shifted to physieochemieal means of measuring the virus. In 1950 Ward of Johns Hopkins adapted a method of measuring the growth of the influenza virus in allantoie fluid to the measurement of a eommon eold virus. Both of these viruses, growing in the allantoic fluid, inerease the rate of synthesis of ribonueleic aeid from simple phosphorus compounds. The allantoic sae of the infected egg is inoeulated with radioaetive phosphorus and, by measuring the rate of ineorporation of radioaetive phosphorus in ribonueleie acid, the amount of virus present may be caleulated.

In summary, Andrewes and other investigators have demonstrated that:

1. The incubation period of the eommon eold is two to three days.

2. The virus is present in greatest abundance twenty-four hours before the onset of symptoms and early in the course of the disease, but has been demonstrated as late as the seventh day. It is present in nasal seeretions and saliva.

3. The mode of transfer appears to be via droplets and fomites; the viruses are not resistant to drying.

4. Andrewes, in eommon with other investigators, has found that only about one-half of those inoeulated develop

colds despite the massive inoculum. Also, deliberate cross infection between subjects occurred very rarely. Both these phenomena are felt to be due to a high level of resistance in the subjects. Indeed, Dr. Pollard of the University of Texas reported in 1948 that subcutaneous inoculation of purified virus made subjects resistant to intranasal instillation of the same virus one week later.

5. By filtration through graded collodion membranes, Andrewes estimates the size of the viruses at 50 millimicrons. Last year, Reagen at the University of Texas published electronographs of a common cold virus 90 millimicrons in diameter and an account of twenty serial subcultures of this virus in egg embryo allantoic fluid.

SYMPTOMATOLOGY AND DIFFERENTIAL DIAGNOSIS

In adults, if the fever rises above 100° or the disease persists for more than 7 days, the disease is not a simple uncomplicated cold.

1. *Allergic Rhinitis*, a commonly confused condition, is characterized by sudden onset, family or personal history of other allergies, a pale edematous "boggy" nasal mucous membrane which later becomes hyperplastic and polypoid, presence of eosinophiles in a nasal smear and a thin clear non-purulent nasal discharge. The diagnosis of allergic rhinitis is usually readily made because of the prolonged course. Differentiation from the common cold is important in younger patients since, if neglected, allergic rhinitis may progress to bronchial asthma.

2. *Acute Undifferentiated Respiratory Disease* is a specific viral antibody-stimulating disease characterized by a fever up to 101°, severe malaise, sore throat, substernal discomfort of variable nature, cough and paucity of nasal discharge.

3. *Non Streptococcal Exudative Tonsillitis* (or pharyngitis) is very similar to acute undifferentiated respiratory disease with the addition of exudate on or about the tonsils or in the oropharynx. No causative bacteria can be demonstrated; a viral etiology is suspected.

4. *In Children* the prodrome of rubeola, rubella, whooping cough, influenza, scarlet fever, meningococcal meningitis and poliomyelitis resembles the common cold.

The familiar clinical features in the adult will not be discussed. However, in infants the common cold shows these variations:

(a) Fever very commonly is as high as 102° to 104° (when convulsions and meningismus may occur).

(b) Diarrhea and vomiting are frequent signs.

(c) Vascular injection of the ear drum is common and should not be confused with otitis media.

(d) Bacterial complications, otitis media, pneumonia, cervical adenitis and retropharyngeal abscess are frequent.

(e) Abdominal pain is frequently present.

TREATMENT

Treatment in adults is symptomatic; analgesics, antitussives and antipyretics are used in endless variety and combinations. Increased fluids and, at times, bed rest may be recommended. Vasoconstrictors should be used only during the later stage when secondary bacterial invasion has made nasal secretions mucopurulent; their purpose is to promote drainage through the ostia of the sinuses as well as to give symptomatic relief.

Treatment of the common cold in infants should be much more active than in adults because of the severe systemic effects and the frequent complications.

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POLIOMYELITIS VACCINE

D. L. SCHATZ, 5T6

EVERY red-blooded man likes a challenge.

One of the greatest challenges to the medical profession over the years has been the production of an effective agent to eradicate poliomyelitis. No other topic has stimulated the press of North America to conduct such an extensive educational campaign toward the public in the past year than the controversial polio vaccine (also known as Salk vaccine after its founder, Dr. Jonas E. Salk of Pittsburgh, Pa.). Last April 96 per cent of all people interviewed in a poll had heard of the vaccine: how much do you as a student of medicine know about the vaccine?

What is Poliomyelitis? A brief description of the disease is helpful in understanding the fundamentals in the preparation and use of the vaccine.

Poliomyelitis is an acute viral disease which, in its most characteristic form, involves various parts of the central nervous system, particularly the motor neurones of the spinal cord, producing varying degrees of weakness and paralysis of voluntary muscles. It was formerly called "infantile paralysis" because 60 per cent of cases occurred in children under four years of age. But, since 1938, statistics reveal that one-third of cases occur in those under 5 years of age, one-third in those from 5 to 14 years of age, and one-third in those over 15 years of age, with a peak incidence at 5 years.

The virus enters the human body via the mouth. Horstmann and Bodian independently demonstrated in 1952, that the virus then pentrates the mucous membrane of the alimentary tract and produces a viremia for a brief period during the prodromal phase. From here the virus progresses to infect the C.N.S.

Clinically there are three types of infection: the least severe or *abortive* type, the more severe or *non-paralytic* type, and the most severe, the crippling *paralytic* type. The majority of cases (80% to 90%) progresses no further than the abortive stage, a mild systemic illness (whose symptoms probably correspond to the viremia), and only a small percentage show involvement of the C.N.S. It may be stated here that authorities do not claim that the polio vaccine will prevent the early gastrointestinal manifestations, but only the C.N.S. involvement. This is a reasonable conclusion since the immunologic barrier established by the vaccine is intended to combat the virus during the viremia, which, as stated above, follows the per-

iod of gastrointestinal infection and precedes C.N.S. invasion.

A Vaccine and a Polio Vaccine. A vaccine is a preparation containing micro-organisms, which, when given to a healthy person, produces in the person an immunization against the disease caused by the organisms from which the vaccine was made. The vaccine elicits an antibody response in the person's serum, hence conveying an artificial immunity to that individual persisting for variable periods of time. There are two kinds of vaccine:

(1) a "live" vaccine, e.g. smallpox vaccine, containing avirulent organisms which are nevertheless still antigenic.
(2) a "dead" vaccine, e.g. T.A.B. vaccine, which is formed with killed organisms which are possessors of antigenicity.

Any vaccine must fulfil four essentials before being regarded as acceptable and useful.

The vaccine must:

(1) be proved harmless in the laboratory and on people.
(2) give rise to antibodies in the recipient's serum.
(3) be standardized in some way to separate good and bad batches.
(4) be proved effective in causing diminution or abolition of the disease.

Safety, to Salk and his colleagues, was a *sine qua non* in the production of the polio vaccine. However, as with any other biological product used in preventive medicine, 100 per cent safety cannot be assured.

Other attempts at immunization against Polio. For many years it has been known that monkeys can be rendered resistant to polio by injection of live virus and some twenty years ago, a number of children were injected with a vaccine prepared from formalinized infected monkey nervous tissue. Many cases of paralysis followed and now, twenty years later, reinvestigation is occurring.

In 1953 Hammond found that gamma globulin containing polio antibodies provides a four to five week period of enhanced protection against the polio virus if given before the stage of viremia. Thus Salk began his preparation of polio vaccine with the reassurance of a proven premise that circulating neutralizing antibodies in the blood are effective in reducing the likelihood of paralysis by polio.

PREPARATION OF THE POLIO VACCINE

To produce a polio vaccine there were two major difficulties to overcome—(1) how to get enough polio virus to make a vaccine and (2) how to kill the virus while preserving its antigenicity. This fastidious polio virus requires living cells for growth and in 1949 Enders, Robbins, Weller and their colleagues in Boston developed human embryonic tissue cultures on which the virus would grow, the first time that the virus had been shown to proliferate in extra-neural tissues. Subsequently Salk demonstrated growth of the virus on monkey kidney tissue.

Selection of strains. There are three Types of polio virus causing infection, consequently all three Types must be included in the vaccine, because immunization against one will not produce it against the other two. Each Type of virus is composed of several strains, the commonest strains causing infection being Brunhilde (Type I), Lansing (Type II) and Leon (Type III). These strains, however, did not produce the most effective vaccine, experiment proved, and so strains Mahoney, MEF-I and Saukett, representing Types I, II and III respectively, were chosen because they ap-

parently produced the highest infectivity titre in tissue culture and were also highly antigenic in monkeys and man. Now it has been shown that these two factors are not necesarily related, and so experiments are being conducted on a vaccine containing strains having high antigenicities but low pathogenicities for monkeys. After last spring's incident of polio induced by the vaccine, the Mahoney Type I strain was criticized as too virulent. Brunhilde Type I was suggested as a substitute and this change is now undergoing investigation.

Growth of Virus. When asked by Dr. Salk to produce the infected culture media for 1954 field trials, Connaught Laboratories in Toronto proceeded to utilize a synthetic nutrient "Number 199" which had been developed previously, under the direction of Morgan, Morton and Parker of Toronto, in a cancer research project. When added to monkey kidney tissue culture media this nutrient was shown by Farrell, Franklin and Parker of Toronto to allow extensive virus proliferation, making possible a vaccine almost free of foreign protein. Monkey kidney tissue cultures are incubated for six days at 37°C., then examined for contamination and compared with standard solutions. If they are satisfactory, they are then seeded with virus of the required Type and returned for four to five days of further incubation.

Inactivation and Safety Testing. Before inactivation each monovalent virus pool is tested for "B" virus and M. tuberculosis. The virus fluid is then filtered to remove resistant virus particles and formaldehyde (formalin) 1:4000 is added and the mixture is again incubated at 37°C. until virtually all the virus is inactivated. Such factors as concentration of formalin, pH of mixture and temperature are maintained at an optimum level calculated to give maximum antigenicity and no infectivity to the vaccine. After three days of reaction about one virus particle out of ten million will remain active, and in an effort to get rid of this the reaction is carried on as long as fourteen days. There is a delicate balance between the amount of formalin required for inactivation of virus and the amount required which will preserve the antigenicity of the virus. Authorities now feel that the virus particles can never be 100 per cent inactivated by formalin but the results approximate 100 per cent so closely that any remaining virus has negligible effects. At two established points during the inactivation process the mixture is tested to see that the virulence is decreasing progressively. After inactivation each monovalent strain is tested for infective virus by tissue culture methods, i.e., 1 cc. from a 1000 cc. batch of vaccine is put in a test tube with monkey kidney tissue and if any live virus persists it will multiply. After pooling of the three monovalent strain vaccines, the trivalent vaccine is tested for infective virus in the same way. The final vaccine pool is also tested for lymphocytic choriomeningitis virus and then for residual active polio virus by intracerebral injections of the vaccine in twelve monkeys which are sacrificed after an interval of thirty days and examined. Any vaccine to be accepted must produce an antibody response in the serum of an inoculated monkey equal to or above a standard level for each of the three Types, and must show no sign of infection.

ANTIBODY RESPONSE

The antibody response elicited by the injection of polio vaccine is influenced by prior immunologic experience, i.e., the individual with previous infection from polio reacts differently immunologically from one with no previous infection because the vaccine acts as a

booster dose in the former. To obtain valid comparisons on the effect of potency and dosage, time, and spacing of inoculations in the production of an effective vaccine, it was necessary for the researchers to know the antigenic response to the vaccine in persons with no previous polio contact. Some of the more fundamental conclusions established from the study of immunologic response to polio vaccine are outlined below:

(1) Subcutaneous, intramuscular and intracutaneous routes of administration have been tried and similar degrees of response were elicited but the mean antibody level was slightly higher with the intramuscular route.

(2) The vaccine is now administered in three doses of 1 ml. each, I.M. or subcutaneously, the second dose following 3-4 weeks after the first and the third dose 7 months after the second.

(3) Antibodies should appear in the serum (in individuals with no previous antibodies) about 7 to 10 days after the first injection.

(4) The antibody response is directly proportional to the dosage up to 1 ml.

(5) Each succeeding dose of the three produces a higher antibody level and the third dose raises the level to a "height of reactivity".

(6) The height of the antibody titre after doses one and two is influenced by the potency and dosage of the vaccine while the level after dose three is influenced by the duration between the second and third doses, the longer the duration (up to 7-10 months) the better the response.

(7) Booster injections given 1-2 years after the third dose (when the antibody level has decreased considerably) cause a dramatic rise in antibody level. Thus, a state of heightened immunologic reactivity persists which is evident on reinoculation or reinfection and likely this reactivity does not decline with time.

(8) Antibody levels from infection are higher than those from vaccination, but after a booster to a vaccinated person, his levels are higher than those of an infected person. Infection in a previously vaccinated person acts as a booster dose.

RESULTS

Field Trials 1954. After Salk had proclaimed his new polio vaccine in 1953, medical authorities studied it and then recommended it for an extensive field trial. The objectives of the trial were:

(1) to see if a formalin-inactivated trivalent polio vaccine could offer protection against naturally occurring polio and, if so, what degree of protection was provided.

(2) to determine what levels of induced antibodies are associated with resistance to paralytic disease.

(3) to observe the nature and incidence of untoward reaction.

Connaught Laboratories in Toronto produced the virus-infected culture media for the Field Trials on request by Dr. Salk. During the trial (children inoculated in the spring of 1954, the study done from June-December 1954):

450,000 children 6-9 years were vaccinated
200,000 children 6-9 years were given placebos
725,000 children 6-9 years were controls

Dr. T. Francis gave the evaluation report on the results of the trial in April 1955. There were one-third to one-quarter as many cases of polio in the vaccinated group as in the control group. Francis stated that the gross calculated degree of protection ranged from 60 to 90 per cent, i.e., 60 to 70 per cent protection against Type I, which causes most paralysis, and 90 per cent or more against II and III. No cases of infective virus appeared in any of the vaccine used. The six year olds got less satisfactory results than did the seven, eight and nine year olds.

1955 Results. The vaccine had proved itself safe and effective. On April 12,

1955 the immunization program began as soon as Dr. Francis' report was made known and six drug houses were licensed for production of the vaccine. Group priority was given to the highest ineidence group first (6-9 years), and then equal proportions of children under 5 years and over 9 years were added. The possibility that the phenomenom of provocation might be involved (i.e., production of polio by the vaccine) was considered by the A.M.A., Public Health Service and other groups, and their conclusion was that "the total preventive effect of the vaccine in a period of rising polio incidence should be much greater than the possible hazard from the provoking effect of the injection".

Tragedy struck shortly after the vaccination program started when many children in California and Idaho developed paralytic polio about one week to ten days after their first injection with Cutter Laboratory vaceine. The number of cases was far in excess of the number that could be expected by chance, while over the rest of the U.S.A. and in Canada there were actually fewer cases than could be expected by ehanee. About 400,00 children were vaceinated with Cutter vaccine before it was recalled and in this group polio struck 79 and 90 others who came in eontact with them. Most of these cases had an upper body paralysis, not lower as is usual, indicating a localization of paralysis to the limbs inoculated. Live Type I virus was isolated from feces of almost every case and also from some of the incriminated lots of Cutter vaccine. The remainder of Cutter's vaccine was recalled and temporary suspension of the whole vaccination program in the United States, but not in Canada, ensued while all six drug companies had their production and testing procedures thoroughly investigated by the United States Public Health Service (PHS). Canadians can point with pride to the fact that no case of vaccine-induced paralysis was demonstrated in Canada. It was decided that the failures of safety on the part of the vaccine lay with the production methods as prescribed by PHS rather than with any deviation from the required procedures. However, with the rigorous testing procedures now established there is little danger of repetition of this incident.

Because the vaccine is not a 100 per cent preventive and also because some children harboured polio virus at the time of vaccination, other cases of polio developed over the summer but in significantly decreased numbers. About 800,000 children were vaceinated in Canada and the total number of cases was about 25 per eent of a five year average. In New York there was a 50 per cent lower rate of paralytic polio among vaccinated children. By mid-September of 1955 statisties compiled for Ontario showed a marked deerease in the number of polio eases as compared with the preceding two years. In 1953, one of the worst years in two decades, there were 1420 eases and 58 deaths; in 1954, one of the best years in two decades, there were 158 cases and three deaths; while this year there had been only 102 cases with one death for a comparable period of time. This number, 102 cases, includes both vaceinated and unvaccinated people of all age groups and no attempt has been made as yet to analyse the number of cases in the vaccinated group and compare it to previous years. It is difficult to evaluate the reasons for a low incidence in 1955 as trends indicate it may well owe to the prevalenee of natural immunity developed after a high incidence year in 1953. It will be two to three years or more before any accurate report can

be presented on the effect of the vaccine in reducing the incidence.

Obstacle Course. Dr. Salk stated that in assessing the state of knowledge of any subject at a particular point in time it is as important to define what is not known as it is to appreciate what is known. The need for continuing study is only too evident when one appreciates the gaps that must be filled in before a thorough knowledge of the vaccine's effect can be obtained. Briefly here are some of the unanswered problems:

(1) The only observed age group in the 1954 trials was 6-9 years and data indicated that the greatest amount of protection occurred among children 9 years old and the degree of effectiveness decreased with age. What changes are necessary to make the vaccine equally effective for all age groups?
(2) Do we have the optimum dosc and interval between injections for the best immunological response?
(3) What is the duration of protection offered by the vaccine?
(4) Will other injections be needed at stated intervals? Salk has observed detectable levels of antibodies for thirty months and more. If booster shots are needed, when should they be given?
(5) Could the vaccine be safely concentrated to enable greater ease of manufacture and improved accuracy in testing?
(6) Can a more stable strain of normal human or primate cells which will grow continuously in cultures be produced and so eliminate the need for monkeys?
(7) Is there a better method of virus inactivation e.g. ultra violet light?
(8) Can the polio vaccine be safely combined with other prophylactic agents as was done with DPT vaccine?
(9) Are we to withhold the vaccine during a polio epidemic, knowing that many morc children will develop paralysis if they are unvaccinatcd, because of the proven danger of an irritant injection localizing paralysis in the inoculated sight? Apparently an intramuscular injection of any vaccine, e.g. DPT, has this effect on occasion, the needle provoking a flare-up by a latent polio infection that otherwise would have done no harm.

One problem that has been settled was a concern that a person vaccinated with a vaccine grown in monkey tissue might be sensitized to Rh antigens. However, tests showed that there are no Rh antigens in the vaccine and so it is assured that they are removed by processing or else completely unrelated to human Rh antigens and so are inconsequential.

In the Crystal Ball. Some authorities feel that the Salk killed-virus vaccine should be abandoned because of its danger of containing infective virus and be replaced by an attenuated live-virus vaccine. The foremost exponent of this theory is Dr. Albert Sabin, a virologist from Cincinnati who believes that we should not wait for years to find out what the best killed-virus vaccine can do but should start now to experiment with attenuated virus vaccines and see what their effect will be. This live-virus vaccine would consist of 3 nonvirulent strains to replace the 3 paralysis-causing strains used in Salk's vaccine. He claims that injection of approximately .001 cc. or swabbing the throat with minute amounts of this vaccine can induce symptomless immunogenic infections—a form of active immunity which, he says, has greater permanence than that induced by Salk's vaccine.

Dr. Joseph Stokes Jr. of Philadelphia is another adherent to the attenuated living virus vaccine clan. He believes that the C.N.S. could be protected with passively transferred antibodies either given parenterally or acquired transplacentally while the individual is exposed by the natural alimentary route to the attenuated living virus vaccine which will not produce paralysis in monkey or man. Study has been carried on for about five years now on this vaccine but it has not yet been accepted for a large scale trial.

Although there are still many obstacles to be overcome and statistics to be evaluated, the effectiveness of the polio vaccine to date is favourably impressive and significant. Only time can provide conclusions about the ultimate effectiveness of the vaccine as a world-wide weapon against poliomyelitis. Probably no other subject has been more conspicuously on the medical horizon or in the lay press so consistently for the past year. However, Dr. Sabin has proferred some sage advice to the world when he states "Let us not confuse this first great victory with total victory".

There is much more to be done.

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ABSTRACTS

Changing Patterns of Resistance of Certain Common Pathogenic Bacteria to Antimicrobial Agents. Finland, M., New Eng. J. Med. **252**: 570, 1955.

For the past several years, the author has collected considerable data on the *in vitro* sensitivity of common pathogenic bacteria to the various antibiotics which have been generally available.

The number of resistant strains of Staph. aureus and the degree of resistance to penicillin and to a lesser extent to chlortetracycline (Aureomycin) and to oxytetracycline (Terramycin) have shown a definite increase. Much of the resistance to oxytetracycline which was observed when this agent first became available may well have been a reflection of cross-resistance from chlortetracycline.

No important changes in resistance to any of the antibiotics have thus far been authenticated by the author for pneumococcus, group A hemolytic streptococcus, meningococcus, gonococcus, H. influenzae and proteus. There appears, however, to have been a definite increase in the sensitivity of strains of gonococcus to sulfadiazine. The author therefore suggests the possibility that during the long period since penicillin has almost completely replaced the sulfonamides in the treatment of gonococcal infection, the gonococci have regained their sensitivity to these agents.

There appears to be a definite increase in resistance of strains of pseudomonas to streptomycin and the broad-spectrum antibiotics and possibly also to neomycin.

The material presented may also be summarized from the point of view of the individual antibiotics. In spite of the intensive use of penicillin, increases in the frequency of resistant strains of bacteria and in the degree of their resistance have been found only for the staphylococcus.

Chlortetracycline and oxytetracycline have been noted to be less effective, particularly against staphylococci, but

whereas Ps. aeruginosa appeared to have increased in resistance to the former, there does not seem to have been a corresponding increase in its resistance to oxytetracycline.

Other workers (Lepper) have shown striking changes in resistance of staphylococci to erythromycin but the author has avoided this by the use of erythromycin in combination with other effective agents.

No major changes in the sensitivity to chloramphenicol, neomycin, bacitracin or polymyxin were noted by the author.

The author then suggests a number of reasons for the changing patterns of resistance of bacteria to antibiotics. The changes may reflect cross-resistance or possibly increased sensitivity resulting from the use of other related or seemingly unrelated agents. Species differences are important among strains of proteus and streptococci. Among strains of Staph. aureus isolated from patients, resistance to penicillin seems to be correlated with the ability of the strains to produce penicillinase. However, most of the important changes appear to be correlated with the extensive use of the particular agent or agents involved, as clearly indicated by increasing resistance of staphylococci to penicillin, chlortetracycline and erythromycin.

Leo Chaikof.

A Re-Evaluation of Sulphonamide Therapy: Yow, E. M. Ann. Int. Med. **43:** 323, 1955.

It was thought for some time that the use of penicillin and the newer antibiotics would eliminate the serious reactions so commonly seen during therapy with the sulphonamides. However, the wide usage of antibiotics has revealed new reactions varying from drug fevers, dermatitis, and blood dyscrasias, to serum sickness, nerve damage, and acute anaphylactic reactions.

Work in the field of sulphonamides in the past few years, with the development of more soluble sulphonamides and of sulphonamide mixtures, has virtually eliminated crystallization as a cause of renal tubular obstruction and hemorrhage. Careful analysis has shown other undesirable side reactions to be in the same range as those due to the antibiotics.

The author points out that, while being less potent agents, the sulphas alter the normal bacterial flora less than do antibiotics, thus reducing the incidence of secondary infection during treatment. The sulphonamides are as effective as antibiotics in the treatment of meningococcal infection and bacillary dysentry, and are usually effective in respiratory tract infection and uncomplicated urinary infections. They are also valuable in combination with antibiotics in the treatment of actinomycosis, pneumococcal meningitis and infections due to H. influenzae and Friedlander's bacillus.

He suggests that the use of sulphonamides in minor infections due to sensitive organisms may delay the development of antibiotic resistant strains and thus reserve the more potent antibiotics for more serious infections.

P. McDougall.

An Epidemic of North American Blastomycosis, Smith, J. G., Harris, J. S., Conant, N. F., and Smith, D. T., J.A.M.A. **158**: 641, 1955.

This paper is a preliminary study of an outbreak of North American blastomycosis occurring in midwestern United States, and is the first culture-proven epidemic ever reported in North

America. The outbreak occurred in Grifton (pop. 1,000) in Pitt County, North Carolina. Between February and June, 1954, eleven cases of blastomycosis were diagnosed, and this paper outlines the epidemiological study of ten. All cases occurred within three miles of the centre of Grifton, as contrasted with a previous incidence of only three cases in all of Pitt County since 1938.

The ages varied from 7 months to 77 years, with 6 cases being 16 years or younger. Six patients were white, 4 were Negro; one half of each were male, half female. All were lung blastomycosis, suggesting air-borne infection. The source of infection could not be traced, but spread from one person to another was ruled out.

Final diagnosis was made in all cases by culture of B. dermatitidis (sputum in 8 cases, lung culture at autopsy in one, gastric washings in one). Smears of these samples were positive in all cases but one. The blastomycin skin test was positive in only 5 of the 10 cases studied, and of the 8 cases in which complement fixation tests were done, only 3 were positive at the time of the epidemic. Erythema nodosum, not previously noted in this disease, was found in three cases.

Of the ten cases studied, one death occurred (the 7-month old infant, who received no treatment), and all others recovered, one without any treatment, and eight treated with Stilbamadine or 2-hydroxystilbamadine.

The eleventh case was discovered at operation for a chronic lung disorder which had flared up in May, 1954, and he was cured by his lobectomy.

B. Langer.

Treatment of Streptococcal Carrier State in a Rural School; Hill, T. B., Amer. J. of Dis. of Children. **90**: 280, 1955.

Constantly recurring hemolytic streptococcal infections in 8 families were traced to the rural school serving these families. This study was carried out to determine if oral penicillin therapy could lower the carrier rate of hemolytic streptococcus in the school population and so decrease the incidence of streptococcal infections. A total of 70 children participated, although the exact number was less than this at any one time.

On Jan. 3, 1955, throat cultures of 59 pupils revealed a carrier rate of 27%. The pupils received a tablet containing 200,000 units of oral, buffered penicillin twice a day for each of the 5 school days of the week for a total of 13 treatment days. None was given on the weekends. A total of 51 pupils started the treatments on Jan. 3, but 4 discontinued before finishing for various reasons. Four additional children received several doses of intramuscular penicillin from their private physicians at the same time, and 3 additional children had received penicillin therapy in the 3 weeks prior to Jan. 3. Thus a total of 58 pupils or 88% of the 66 then in attendance received some form of treatment.

Cultures were repeated on Jan. 26, 1955, six days after completion of therapy and 3 of 56 pupils, or 5%, were positive. One had received no treatment, one had interrupted treatment because of fever, and only one had received the full course.

Cultures were repeated 3 months later and 8 of 64 pupils, or 12%, were positive. All of these still had their tonsils and adenoids present, although 18 of the 70 children who participated had had previous tonsillectomy and adenoidectomy. Whether this would have been true with carefully taken nasopharyngeal swabs would be important in considering whether tonsillectomy

and adenoidectomy would be an adequate means of treating a chronic carrier.

The positive cultures were found only in those children who had been chronic carriers previously. Either these were being reinfected by people outside the school, or a biological cure was not obtained by the treatment, but the streptococcal colonies were so reduced in number as not to be obtainable by throat swab.

L. CHARENDOFF.

OF CURRENT INTEREST

Dr. R. I. Harris was made an Honorary Fellow of the Royal Australasian College of Surgeons while he was in Sydney last August.

Dean J. A. MacFarlane was awarded an Honorary Doctora by the University of Brazil. It was conferred on him last November when he was in Brazil.

Professor R. C. Dickson has been appointed Professor of Medicine at Dalhousie University. He will take up his appointment on January 1, 1956.

A Refresher Course in Eye Surgery has been arranged by the Department of Ophthalmology for three days, from March 26–28, 1956. The guest lectures will be:

Dr. Conrad Berens—New York University, New York City. Dr. Philip Meriwether Lewis—University of Tennessee, Memphis. Dr. Harold G. Scheie—University of Pennsylvania, Philadelphia.

The following awards have been made:

The Baptie Scholarship
G. S. Conn (II Med. Yr.)

The B'Nai B'Rith Scholarship
P. E. Perry (II Med. Yr.)

Medical Alumni Assoc. Scholarship
M. F. Zane (2nd Premed. Yr.)

Medical Alumni Assoc. Scholarship
R. D. Bethune (II Med. Yr.)
A. Teglas (II Med. Yr.)

Medical Alumni Assoc. Scholarship
R. I. Hector (III Med. Yr.)

Medical Alumni Assoc. Scholarship
W. F. Neale (IV Med. Yr.)

The Charles E. Frosst Scholarship
A. S. Trimble (IV Med. Yr.)

RECENT ACCESSIONS TO THE MEDICAL READING ROOM

American Association for the Advancement of Science: Sex in microorganisms. 1954.

Bailey, F. R.: Text-book of histology. 13 ed. 1953.

Biochemical preparations. v. 4, 1955.

Burch, G.: A primer of electrocardiography. 3rd ed. 1955.

Clark-Kennedy, A. E.: Medicine in its human setting. 1955.

Colowick, S. P.: Methods in enzymology. v. 1, 1955.

Ergonomics Research Society: Symposium on fatigue, ed. by Floyd. 1953.

Gaddum, J. H.: Polypeptides which stimulate plain muscle. 1955.

Gill, M. M.: The initial interview in psychiatric practice. 1954.

Gray, C. H.: Clinical chemical pathology. 1954.

Gurd, F. R. N.: Chemical specificity in biological actions. 1954.

Hunter, D.: The diseases of occupations. 1955.

Jawetz, E. M.: Review of medical microbiology. 1955.

Ledermann, E. K.: Natural therapy. 1953.

Lewis, G. M.: Practical dermatology for medical students. 1952.

Lichenstein, B. W.: A textbook of neuropathology. 1949.

Longerich, M. C.: Aphasia therapeutics. 1955.

National Cancer Institute of Canada. Canadian Cancer Conference. v. 1, 1955.

Nuffield Provincial Hospitals Trust: Studies in the functions and design of hospitals. 1955.

Peele, T. L.: The neuroanatomical basis for clinical neurology. 1954.

Racker, E.: Cellular metabolism and infections. 1954.

Robinson, F. A.: The vitamin B complex. 1951.

Sorsby, M.: The National Health Service. 1953.

Symposium on Present Problems in Nutrition Research, Basel, 1952. Gegenwartsprobleme der Ernahrungsforschung. 1953.

Verrey, F.: Clinique de l'humeur aqueuse pathologique. 1954.

Weinemann, J. P.: Bone and bones. 2 ed. 1955.

White, J. C.: Pain its mechanisms. 1955.

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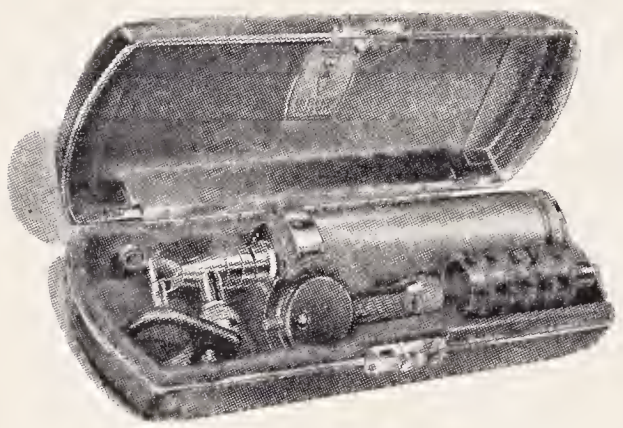

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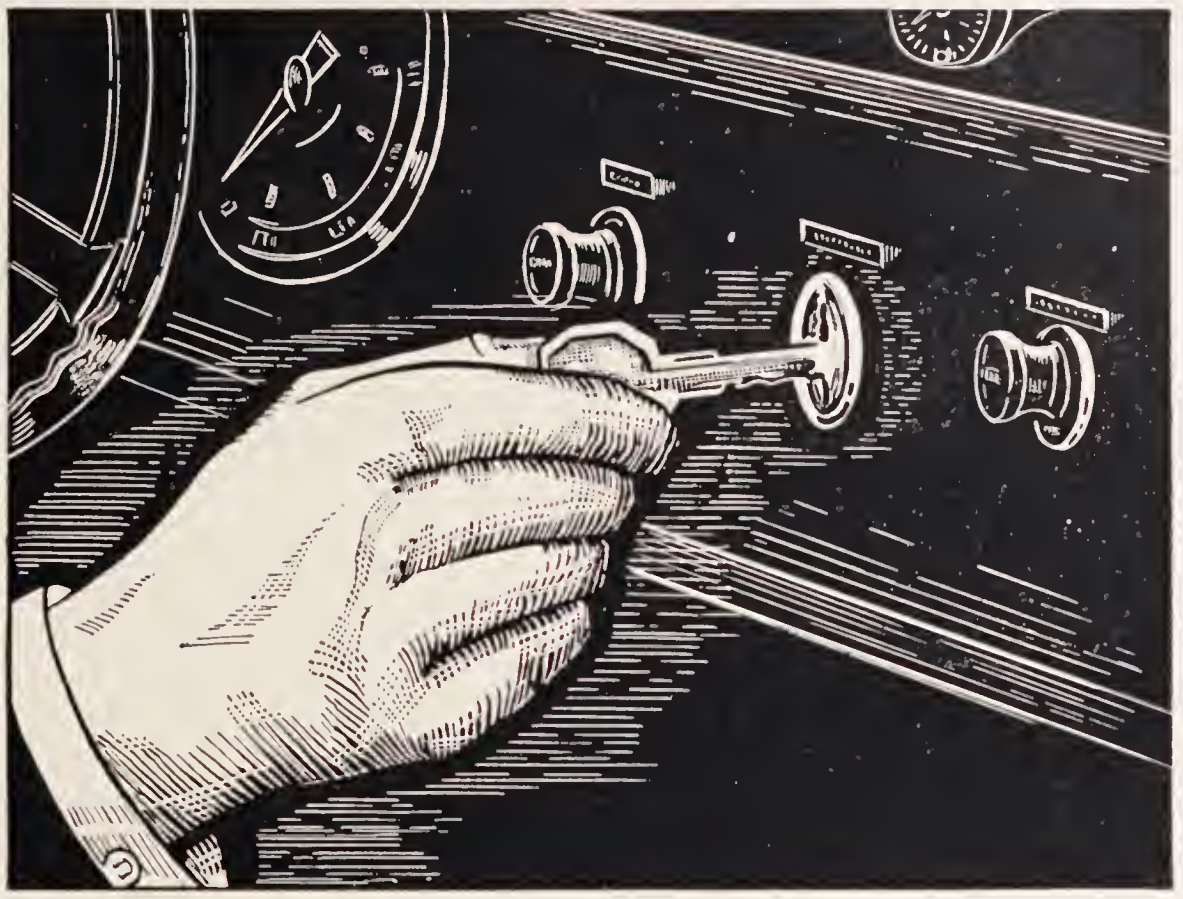

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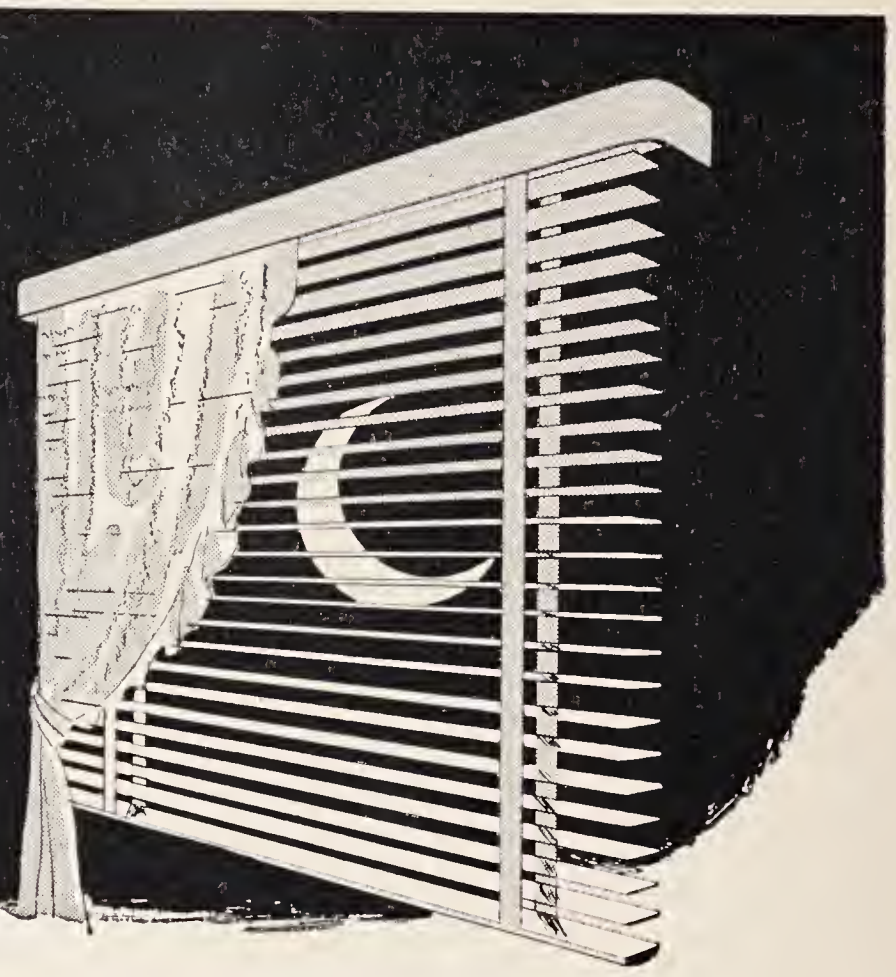

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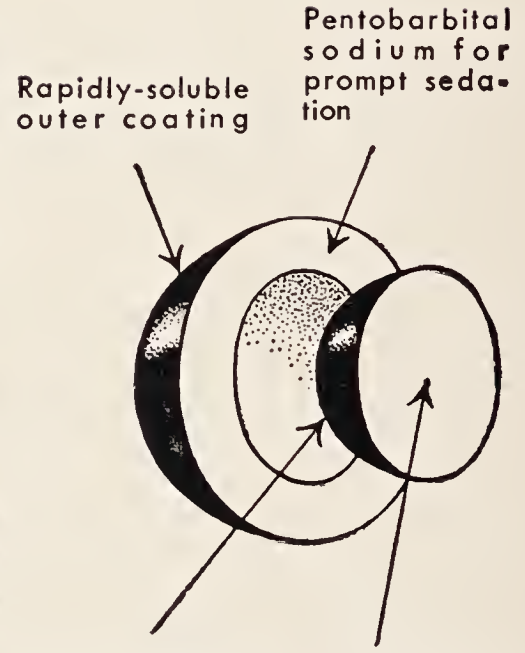
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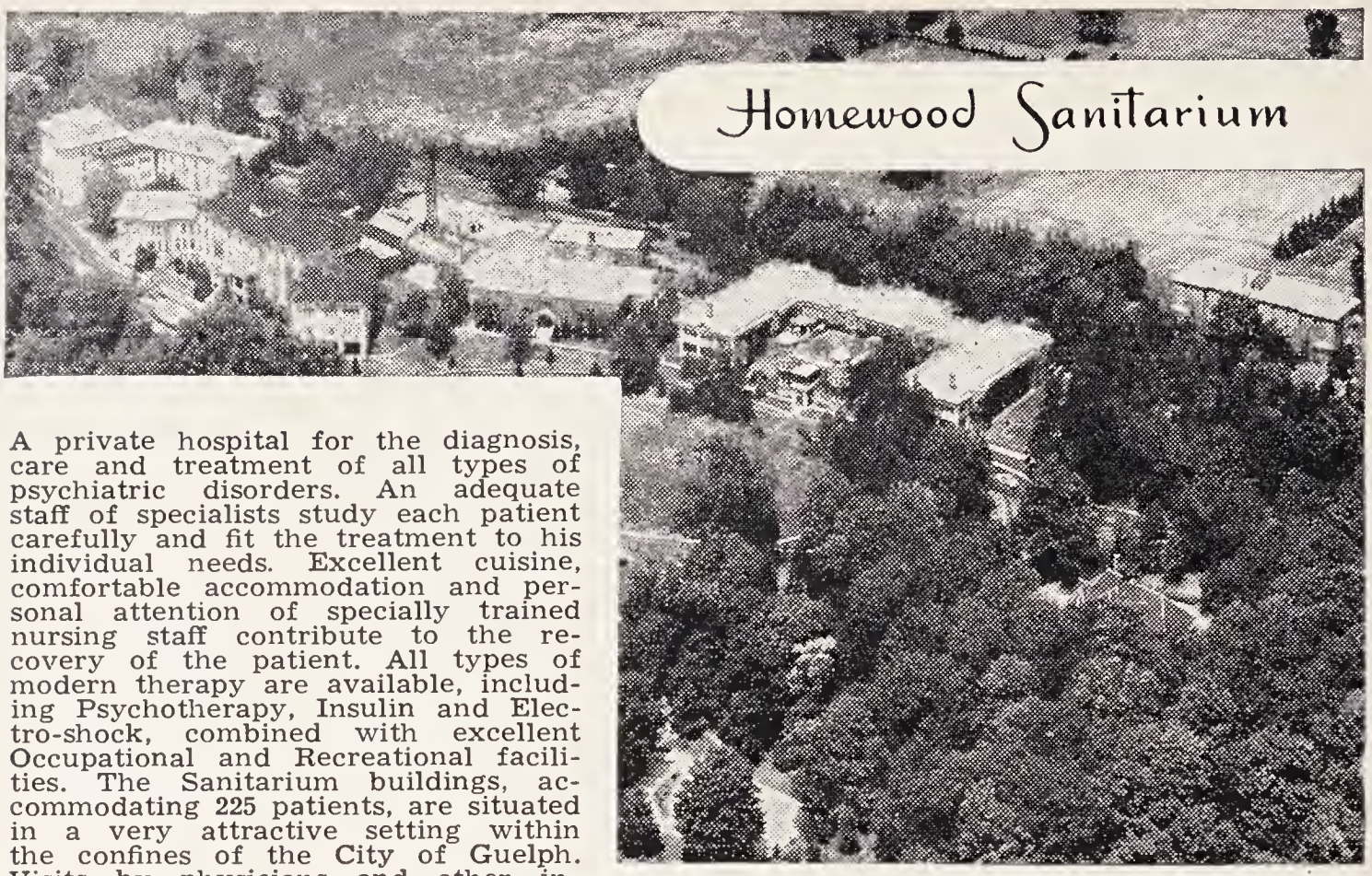

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Danger without signals. Trichomonads in the male rarely produce symptoms to signal their presence.

Prevent re-infection. Karnaky recommends in recurrent cases that the husband wear a condom during coitus for four to nine months. By the end of this time the trichomonads will usually die out. Davis states: Use of a sheath by the husband has long been advised during the period a woman is under treatment and should be used permanently if he carries the infection.

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the husband. In prescribing a condom, be selective as to quality and take advantage of Schmid product improvements.

Prescribe protection. Take specific measures to win the co-operation of the husband in your treatment of vaginal trichomoniasis. Otherwise he may re-infect the patient and nullify the good results of the regimen. Any husband or wife in your practice would most likely prefer to hand the druggist your prescription for a condom, rather than to ask for it "in public." This is another instance of diplomacy in medicine to prevent an embarrassing situation. To assure finest quality and earn appreciation for your thoughtfulness, prescribe condoms by name. Prescribe Schmid protection for as long as *four to nine months* after the wife's infestation has cleared. The protection Schmid condoms afford is the very foundation of re-infection control.

References: 1. Karnaky, K. J.: Urol. & Cutan. Rev. 48:812 (Nov.) 1938. 2. Whittington, M. J.: J. Obst. & Gynaec. Brit. Emp. 58:614 (Aug.) 1951. 3. Freed, L. F.: South African M. J. (March 27) 1948, as abstracted in Urol. & Cutan. Rev. 52:489 (Aug.) 1948.

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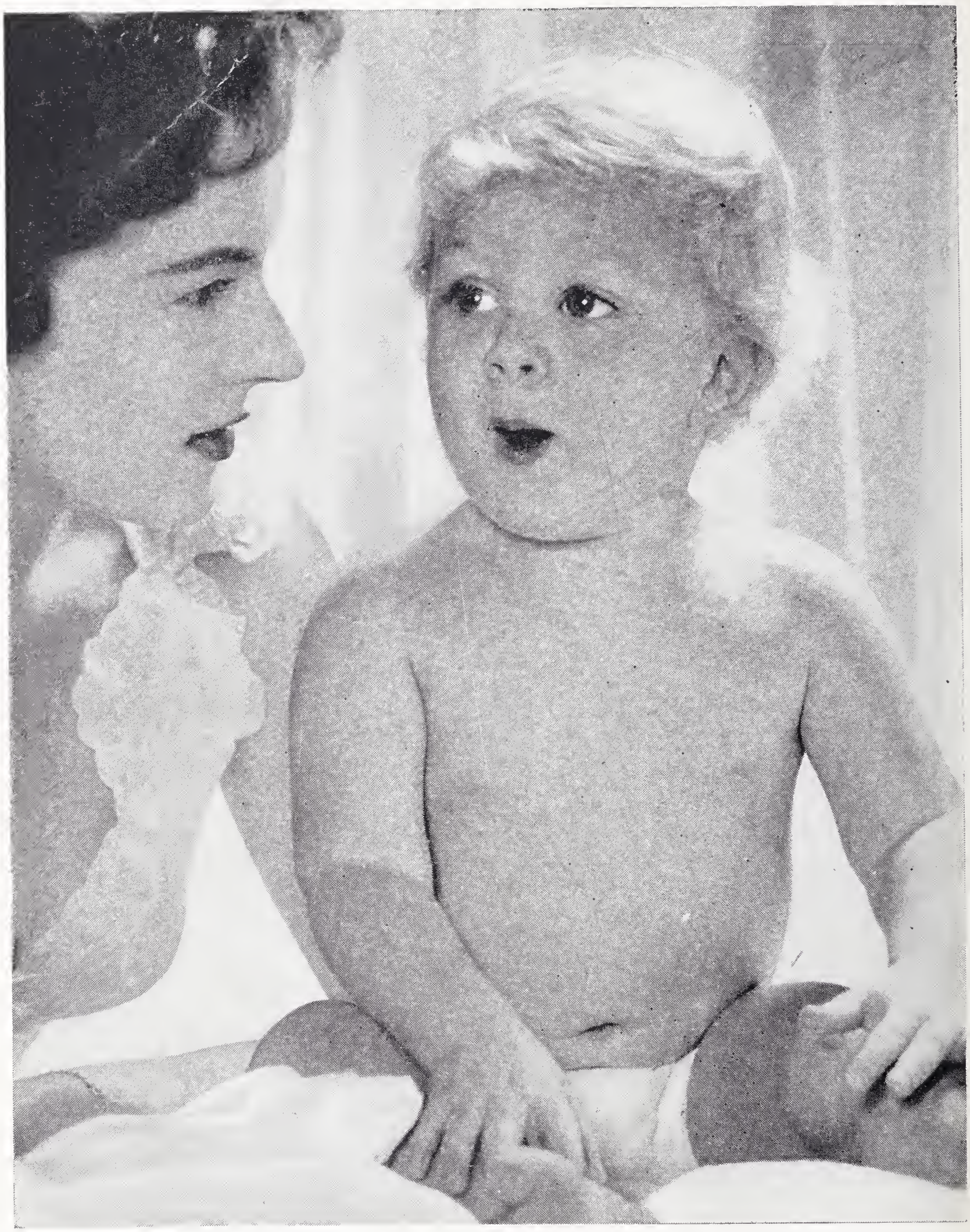

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